STEPHEN P. SWINTON (106398)
J. CHRISTOPHER JACZKO (149317)
COOLEY GODWARD LLP
4401 Eastgate Mall
San Diego, CA 92121-2128
Telephone: (858) 550-6000
Facsimile: (858) 550-6420

R. WILLIAM BOWEN, JR. (102178)
GEN-PROBE INCORPORATED
10210 Genetic Center Drive
San Diego, CA 92121-4362
Telephone: (858) 410-8918
Facsimile: (858) 410-8637

Attorneys for Plaintiff
GEN-PROBE INCORPORATED

UNITED STATES DISTRICT COURT

SOUTHERN DISTRICT OF CALIFORNIA

GEN-PROBE INCORPORATED,

Plaintiff,

v.

VYSIS, INC.,

Defendant.

No. 99CV2668 H (AJB)
THE HONORABLE MARILYN L. HUFF

PLAINTIFF GEN-PROBE INCORPORATED'S MEMORANDUM OF CONTENTIONS OF FACT AND LAW

[Local Rule 16.1 (f)(3)]

Pre-Trial Conference: February 4, 2002
Time: 10:30 a.m.
Place: Courtroom 1

TABLE OF CONTENTS

TABLE OF CONTENTS
(CONTINUED)

PAGE

TABLE OF CONTENTS
(CONTINUED)

PAGE

TABLE OF CONTENTS
(CONTINUED)

PAGE

TABLE OF AUTHORITIES

PAGE(S)

CASES

TABLE OF AUTHORITIES
(CONTINUED)

PAGE(S)

TABLE OF AUTHORITIES
(CONTINUED)

PAGE(S)

TABLE OF AUTHORITIES
(CONTINUED)

PAGE(S)

TABLE OF AUTHORITIES
(CONTINUED)

PAGE(S)

STATUTES

TABLE OF AUTHORITIES
(CONTINUED)

PAGE(S)

OTHER AUTHORITIES

I. INTRODUCTION

Plaintiff Gen-Probe Incorporated ("Gen-Probe") submits this Memorandum of Contentions of Fact and Law pursuant to Local Rule 16.1(f)(3) and the Court's December 6, 2001 Order Granting Vysis, Inc.'s Ex Parte Motion for Continuance of the Final Pre-Trial Conference and Associated Deadlines.

II. CONTENTIONS OF FACT

A. THE PARTIES

1. Gen-Probe was founded in San Diego, California in 1984 as a small "start up" company, seeking to develop products based on the discoveries of a local research scientist. Gen-Probe has grown over time to become one of the largest biotechnology companies in San Diego. Gen-Probe maintains its principal offices and research facilities at 10210 Genetic Center Drive, San Diego, California 92121, where it employs over 500 scientists and staff. Gen-Probe is organized under the laws of the State of Delaware.

2. Defendant Vysis, Inc. ("Vysis") was formed in 1991. Vysis is the successor to Gene-Trak Systems, Inc. As used herein, "Vysis" refers to Vysis and to its predecessors-in-interest, including Gene-Trak Systems. Vysis is engaged in the business of developing products used in the evaluation of genetic diseases and maintains its principal place of business in Downers Grove, Illinois. Vysis is organized under the laws of the State of Delaware. Until December 2001, Vysis was controlled by BP Amoco, Inc. Vysis is now a wholly-owned subsidiary of Abbott Laboratories, Inc.

B. BACKGROUND REGARDING THE TECHNOLOGY AT ISSUE

3. Living cells store genetic information in molecules of nucleic acid known as DNA. These molecules consist of long, thin strands that, in turn, are usually found in the form of two tightly bound, complementary chains. DNA molecules contain their genetic information in the form of a genetic code. The information in the DNA determines the life processes of each organism. DNA is used to make related nucleic acid molecules called RNA, which are used to transfer the information to cell components that manufacture proteins that are used to determine the structure and function of the cell.

4. Through the work of its scientists and staff, Gen-Probe has developed and continues to develop diagnostic tests that seek out the DNA or RNA of infectious organisms. These types of tests are generally referred to as "genetic probe tests" or "nucleic acid tests" ("NAT"). Gen-Probe now markets DNA probe products that test for a wide range of microorganisms that cause tuberculosis, strep throat, pneumonia, fungal infections and sexually transmitted diseases. Through the efforts of its scientists and staff, Gen-Probe has emerged as a recognized world leader in the development, manufacture and commercialization of diagnostic products based on its patented genetic probe technology. Gen-Probe has received over 40 FDA clearances and approvals for genetic probe tests to detect a wide range of microorganisms, including *Chlamydia trachomatis, Mycobacterium tuberculosis*, and *Neisseria gonorrhoeae*.

5. Many human diseases are caused by bacterial or viral agents that invade living cells. Most often, the presence of these bacterial or viral agents was detected directly by growing them in culture or indirectly through the detection of antibodies. Unfortunately, it takes time, sometimes weeks or months, to isolate organisms in culture, and it usually takes months for the body to manufacture antibodies in sufficient amounts to reveal the presence of infectious agents. Consequently, these methods do not lend themselves to early detection of infection. NAT addresses this problem.

6. Among the disease detection technologies recently applied by Gen-Probe in its NAT products is its patented nucleic acid technology known as "Transcription-Mediated Amplification" ("TMA"). This technology enables Gen-Probe's NAT products to detect extraordinarily small quantities of the nucleic acids of infectious agents.

7. In September 1996, Gen-Probe received a $7.7 million grant from the National Institutes of Health to develop TMA-based nucleic acid tests to be used in screening donated blood for human immunodeficiency virus (HIV), the causative agent of AIDS, and hepatitis C virus (HCV), which causes a severe form of hepatitis.

8. At the time of the NIH grant to Gen-Probe, donated blood was principally tested by procedures that detected the presence of antibodies to the viruses being screened. Due to the time it takes for the body to make antibodies after initial infection, donated blood may test negative for

antibodies, yet still carry infectious viruses. This delay between the time of actual infection and the time that antibodies can first be detected is often known as the "window period." Reduction of this "window period" was a significant concern of the United States government and the primary focus of the grant to Gen-Probe to develop NAT diagnostics for use in blood screening.

9. In fulfilling its obligations under the grant, Gen-Probe developed NAT tests to detect the nucleic acids of HIV and hepatitis C virus in blood. Through the use of its NAT test, Gen-Probe believes that researchers and medical personnel will be able to rapidly and *directly* detect the presence of genetic material of viruses like HIV and HCV more accurately. As such, Gen-Probe believes that its new test may significantly reduce the "window period" for detection of these extremely harmful viral agents and resulting diseases.

10. Final development of the NAT tests for blood screening in the United States is now taking place in testing conducted by the American Red Cross, America's Blood Centers, and others. Use of the tests in the United States is made pursuant to an Investigational New Drug Application filed with the United States Food and Drug Administration. In blood tested by the American Red Cross, Gen-Probe's products have detected hepatitis C virus and HIV which escaped detection by prior methods.

11. Gen-Probe has entered into an agreement with Chiron Corporation ("Chiron") of Emeryville, California, with respect to the development, manufacture, and distribution of blood screening products. Gen-Probe is also a party to an agreement with Bayer Corporation ("Bayer") of Emeryville, California with respect to the development, manufacture, and distribution of clinical diagnostic products for the detection of HIV and hepatitis C virus, among other pathogens.

12. All of the Gen-Probe products are manufactured in San Diego, California.

C. THE '338 PATENT

13. The United States Patent and Trademark Office issued United States Patent No. 5,750,338 (the "'338 Patent") on or about May 12, 1998. The '338 patent was based upon United States Patent Application No. 08/238,080, which was filed on May 3, 1994.

14. Vysis claims to be the owner, by assignment, of the entire right, title and interest of the '338 patent. Vysis contends the '338 patent has a priority date of December 21, 1987.

15. The '338 patent relates generally to methods for use in nucleic acid diagnostics, including the use of nucleic acid "probes" to detect infectious organisms. In particular, the '338 patent relates to methods by which scientists may "capture" nucleic acid molecules onto solid supports and copy (or "amplify") those molecules so that small quantities of these molecules then may be detected by probes. The scientific concepts relevant to this require an understanding of nucleic acids and nucleic acid probes as well as techniques for target capture and amplification.

16. In relation to the '338 patent, as of December 21, 1987 one of ordinary skill in the art would be considered to have been an individual with a postgraduate degree in the biological sciences and 5 to 7 years relevant post-graduate research experience in molecular biology. Such experience would have allowed the individual to develop the skills of a molecular biologist using the techniques of DNA and RNA isolation and characterization, cDNA synthesis, cloning, liquid and solid phase hybridization, isotopic and non-isotopic labeling methods, DNA sequencing methods, and nucleic acid amplification.

1. Nucleic Acids

17. Nucleic acids are molecules that store and transfer genetic information in all living organisms. The two main types of nucleic acids are DNA (deoxyribonucleic acid) and RNA (ribonucleic acid). DNA functions as a stable repository of genetic information, while RNA typically serves to transfer the information stored within DNA to the cell's machinery for making proteins.

18. DNA and RNA are both composed of chains of chemical sub-units called "nucleotides." Each nucleotide has three components: a sugar, a phosphate group, and a "base" containing nitrogen. There are four types of nucleotides in DNA, each of which has a different base: adenine, thymine, guanine, or cytosine (abbreviated A, T, G, and C). The nucleotides in RNA are A, G, C and uracil (U).

19. The "sequence" of the individual A, T, G, and C nucleotides in a DNA molecule encodes the genetic information that instructs the cell how to make particular proteins. Because DNA sequences determine which proteins a cell will make, it is differences in their DNA sequences that make the cells of one organism differ from the cells of another.

20. DNA in cells ordinarily occurs in a molecular structure in which two "strands" of DNA are specifically bound to one another in a structure that resembles a twisted ladder. In double-stranded DNA, the nucleotides on opposing strands of the ladder are always paired in a precise way. An "A" nucleotide binds only to a "T" nucleotide on the opposite strand, and vice versa. Likewise, a "G" nucleotide binds only to a "C" nucleotide, and vice versa. Each combination of an "A" nucleotide with a "T" nucleotide (or a "C" with a "G") is referred to as a "base pair." The way in which each type of nucleotide binds only to one other type of nucleotide is called "complementary base pairing." As a result of complementary base pairing, the sequence of nucleotides on one strand of a DNA molecule necessarily determines the sequence of nucleotides on the opposite strand. Complementary base pairing is substantially the same for RNA, using "C" paired with "G" and "A" paired with "U."

2. Nucleic Acid Probes

21. By exploiting the natural feature of complementary base pairing, scientists can use pieces of nucleic acid as "probes" to detect the presence of a target nucleic acid in a test sample. If two complementary pieces of nucleic acid are present in a solution under the right conditions, the complementary bases will bind together or "hybridize" to form double strands. This phenomenon is commonly known as "nucleic acid hybridization." Nucleic acid hybridization techniques can be applied in a diagnostic test to detect an infectious organism (the "target" organism) by the use of a probe that is designed to be bind specifically to a nucleic acid sequence that is known to be unique to the target organism.

22. In theory, if the target organism is present in the sample, the "probe" should bind to the target organism's nucleic acids because the sequence of the probe has been designed to be complementary to it. By attaching a detectable "label" to a probe, scientists are then able to determine how much, if any, probe has bound to sequences from the target organism.

3. Target Capture

23. Target capture techniques are used in nucleic acid methods to isolate a particular nucleic acid of interest prior to detection or other steps. In target capture methods, the target nucleic acid is bound to a solid support, such as a filter, particle, or a bead, which allows the target

to be separated from the rest of the sample. The immobilized target nucleic acid is detected with a probe, amplified prior to detection, or used for other purposes.

24. The target nucleic acid can be immobilized on the solid support either by direct attachment or by the use of a "capture probe" or other intermediary that forms a bridge between the support and the target nucleic acid. A capture probe is a nucleic acid sequence that is designed to bind with the target organism's DNA or RNA and also attach to the solid support.

4. Amplification

25. Often, it is necessary to detect very small numbers of infectious organisms in a sample. This is particularly true when screening for the presence of the organism in the absence of a full-blown infection. Examples include screening blood intended for transfusion for the presence of viruses such as HIV. In these situations, the presence of even small numbers of organisms may lead to the transmission of infection from one individual to another.

26. The classic way to detect low numbers of organisms is to transfer the sample to culture media that will support the growth of the organism. After a suitable time, the number of organisms will generally have increased sufficiently to allow them to be detected directly by hybridization or other methods. Growing organisms in culture is slow, costly, and inconvenient, and some important pathogenic organisms cannot be cultured in the laboratory. A better approach is to rapidly increase the target organism's nucleic acid in the laboratory through processes known as "nucleic acid amplification." Amplification procedures are generally performed with enzymes and primers. Enzymes are protein molecules that catalyze biological reactions. "Polymerase" enzymes are used to copy a DNA or RNA strand to make its complement and occur naturally in cells. These enzymes are normally used in cellular processes to make copies of genes to be passed on to its progeny. Polymerase enzymes may be either specific or non-specific in the manner in which they copy nucleic acids.

27. Scientists have learned to use enzymes such as polymerase to increase the amount of a DNA or RNA in sample up to a billion-fold in a matter of minutes. By making multiple copies of the target organism's nucleic acids, the amount of target that is available to bind with a probe in a detection step is increased to easily detected levels, thus increasing the "sensitivity" of

the assay.

28. Primers are used in amplification processes to provide starting points for the synthesis of nucleic acids by enzymes such as polymerase The primers used in amplification processes can be either specific or non-specific. "Specific" primers are carefully designed to bind only to a pre-selected nucleic acid sequence of a particular target organism, usually a sequence selected to be unique to that organism. Non-specific or "random" primers can be used with DNA polymerases to copy random portions of any nucleic acid sequence in the target organism. When random primers are used, the resulting amplification process is referred to as "non-specific" because DNA synthesis begins at random locations all over the target nucleic acid. Other non-target nucleic acids that may be present in the sample are also amplified. Using random, non-specific primers avoids the work required to select, make, and test specific primers for each individual target organism.

29. The Court has previously construed the claims of the '338 patent to encompass only non-specific amplification.

D. GEN-PROBE'S PRODUCTS DO NOT INFRINGE THE '338 PATENT

30. Gen-Probe's NAT test kits for use in detecting HCV and HIV in the nation's blood supply, which utilize Gen-Probe's own patented Transcription Mediated Amplification ("TMA") method, do not and will not infringe any valid claims of the '338 patent.[1]

31. Vysis has asserted that Gen-Probe's products infringe claims 1, 2, 3, 4, 5, 7, 8, 9, 10, 11, 13, 14, 24 and 25. Claims 1, 2, 3, 4, 5, 7, 8, 9, 10, 11, 13 and 14 are method claims that are directly infringed only in the practice of the method. Claims 24 and 25 are apparatus claims to a kit. However, as set forth below, those claims are written in means-plus-function format under 35

[1] At the time it filed its complaint, the only commercial products that Gen-Probe was distributing that incorporated any type of target capture and nucleic amplification consisted of its NAT test kits for detecting HIV and HCV. Since that time, however, Gen-Probe has begun distribution of its Aptima Combo 2 kits for detection of sexually transmitted disease. From a structural and theoretical perspective, both types of products perform in a similar manner. As such, any reference to Gen-Probe's NAT products for HIV and HCV should apply equally to Gen-Probe's Aptima Combo 2 products and any judgment of non-infringement should apply to those products as well.

U.S.C. § 112, paragraph 6.

1. The structure and performance of Gen-Probe's NAT test kits

32. Gen-Probe's NAT test kits incorporate an independently patented target capture methodology and a proprietary and independently patented specific amplification technique generically termed "TMA." Although numerous bases exit to distinguish Gen-Probe's products, the following contentions of fact establish that Gen-Probe's use of TMA amplification in those products singularly establishes that Gen-Probe's products do not infringe the '338 patent under the doctrine of equivalents.

33. Although Gen-Probe contends that the generic differences between TMA and the non-specific amplification techniques claimed in the '338 patent independently establish the lack of equivalence of Gen-Probe's products, the significant enhancements that Gen-Probe has designed into its practicing embodiments of TMA are particularly significant here for two reasons. To begin with, in order to satisfy its burden of proof that Gen-Probe's products infringe the '338 patent, Vysis must prove that the products -- *as designed and practiced* -- infringe. Accordingly, proof that "generic" TMA cannot infringe the '338 patent is sufficient for a judgment of *non-infringement* in favor of Gen-Probe. However, for Vysis to sustain its burden of proof of infringement, it must show that the *particular* embodiments of TMA as practiced in Gen-Probe's accused products infringe.

34. Vysis cannot satisfy that obligation for several reasons. Fundamentally, the embodiments of TMA practiced in Gen-Probe's products represent significant refinements and advances over "generic" TMA and those differences further establish the lack of equivalence. Since the time Gen-Probe scientists invented TMA, tens of thousands of person-hours have been devoted to refining general TMA to the particular embodiment practiced in Gen-Probe's products.

35. From a procedural basis, Vysis' expert admits that he has not examined the embodiments of TMA that Gen-Probe has employed in its products nor reviewed the relevant product literature associated with those products. Because Vysis and its expert hold the burden of proof on this issue, they cannot meet that burden by reason of this fundamental lack of evidence and proof.

36. Gen-Probe's accused products consist of packaged kits that consist of reagents, enzymes, target capture beads and nucleic acid capture probes all specifically constructed and designed for detection of specified nucleic acid targets comprised in targeted pathogenic organisms. Pursuant to FDA regulations, Gen-Probe includes within each kit a detailed package insert that provide detailed and precise instructions for the performance of the diagnostic procedure using those constituent components.

37. All of the enzymes and other constituent components contained in Gen-Probe's products have non-infringing uses. Thus, as to the asserted method claims, Gen-Probe only has liability for "indirect" infringement where its customers use its kits as specifically directed in accordance with the detailed instructions contained on the package inserts.

2. Amplifying the Target Polynucleotide

a. Gen-Probe's TMA Method Does Not Perform Substantially The Same Function as Non-specific Amplification Methods

38. As mentioned above, the Court has previously construed the claims of the '338 patent to encompass only non-specific amplification. Vysis has admitted that Gen-Probe's TMA products do not use non-specific amplification methods and the court has granted partial summary judgment on the issue of literal infringement. Therefore the only remaining issue in the case is whether Gen-Probe's blood screening assay infringes the '338 patent under the doctrine of equivalent. Gen-Probe denies such infringement. There are substantial differences between Gen-Probe's TMA method and the non-specific amplification methods described and claimed in the '338 patent, when considered as separate elements and when considered in the "context of the claims" under the "all elements rule." TMA does not perform substantially the same function in substantially the same way to achieve substantially the same result as the non-specific methods of amplification encompassed by the claims of the '338 patent.

39. Specific amplification techniques, in general, and TMA in particular, function much differently than do non-specific amplification techniques. Gen-Probe's TMA amplification method, like other specific amplification techniques such as the Polymerase Chain Reaction ("PCR"), uses specific primers that attach to carefully selected portions (or "sequences") of the

target organism's nucleic acids. These sequence-specific primers are carefully researched and designed to attach to unique nucleic acid sequences of the target organism, so that the test produces accurate results. Non-specific amplification methods use "random" primers rather than "specific" primers.

40. Gen-Probe's TMA method functions to exponentially increase both the ***absolute*** and ***relative*** amounts of a particular nucleic acid sequence of interest in a mixture of nucleic acids. In direct contrast, non-specific amplification functions only to increase the absolute amount of *all* nucleic acids present in a sample and does ***not*** increase the relative amount of a particular nucleic acid sequence of interest.

41. Specific amplification is useful for diagnostic purposes even without a target capture step. In contrast, non-specific amplification is *not* a viable diagnostic method because it does not increase the amount of a target nucleic acid relative to other nucleic acid sequences.

b. Gen-Probe's TMA Method Does Not Perform In Substantially The Same Way as Non-specific Amplification Methods

42. The enzymes and primers used in any amplification process can be specific or non-specific. The primers used in Gen-Probe's specific TMA amplification method have been carefully selected by Gen-Probe's scientists and are generally designed to bind to specific, unique sequences in a DNA or RNA molecule. In amplification processes, sequence-specific primers and enzymes such as those used in TMA play a role substantially different from non-specific primers and enzymes. This fact is well known to those of ordinary skill in the art. For example, specific primers and enzymes can function together to amplify a target nucleic acid only if the specific sequence of interest bound by the primer and/or recognized by the enzyme is present in the sample.

43. By contrast, non-specific primers and enzymes will amplify *any* and *all* sequences present in the sample. The random primers will potentially bind to all of the sequences in the sample and non-specific replication enzymes will catalyze DNA or RNA synthesis at points throughout the entire lengths of the nucleic acid molecules present without regard to sequence.

44. In its TMA method, Gen-Probe uses two amplification enzymes that depend upon

the presence of specific primers. One of these enzymes is reverse transcriptase ("RT"). RT is a DNA polymerase that produces a complementary DNA strand copy of a single-stranded RNA or DNA that has a bound primer. In TMA, RT produces complementary DNA from the target nucleic acids (or their complementary strands) only if the sequence-specific primers first bind to a single strand of RNA or DNA. That is, if the target organism is not present in the sample, the primers will be unable to bind to the target sequence and the RT will not initiate synthesis.

45. Another specific primer used in Gen-Probe's method includes a specific "promoter" sequence that is recognized by another enzyme ("T7 RNA polymerase") that binds specifically to that promoter sequence to produce many RNA copies by transcription[2]. A functional "T7 promoter" is formed in the course of the TMA process if, and only if, (1) the primer finds and binds to its complementary target sequence in the captured target molecule so that the target sequence is copied by reverse transcriptase and (2) the second primer binds to the newly synthesized DNA and DNA polymerase makes the complementary DNA strand. If this double-stranded, and hence functional, T7 promoter *is* formed as a result of these *two* primer binding and extension processes, then the T7 RNA polymerase used in Gen-Probe's HIV/HCV test will amplify the sequence attached to the T7 promoter sequence. Significantly, the T7 RNA polymerase does not amplify other sequences present in the sample because they are not attached to a T7 promoter sequence.

46. In Gen-Probe's HIV/HCV test, the T7 polymerase enzyme *specifically* recognizes the T7 promoter sequence, which has been *specifically* attached to the target sequence by the binding and replication of *specific* primers, and the T7 polymerase *specifically* amplifies the target sequence starting only from that T7 promoter sequence. The process repeats in a cyclic fashion, amplifying the particular target sequence of interest. Gen-Probe's amplification method therefore safeguards against amplification of non-target sequences and thus protects against false positive results. In contrast, non-specific amplification methods amplify all sequences in the sample. Thus, TMA functions in a way that is substantially different than the way in which non-specific

[2] "Transcription" is the process of making single-stranded RNA copies of sequences present in a strand of DNA.

amplification functions.

c. Gen-Probe's TMA Method Does Not Produce Substantially The Same Results as Non-specific Amplification Methods

47. The results obtained from Gen-Probe's method are also substantially different than the results achieved by non-specific amplification methods.

48. First, specific amplification methods result in the increase in a particular nucleic acid sequence, in both ***absolute*** and ***relative*** terms. On the other hand, non-specific amplification does not achieve an increase in the amount of a particular nucleic acid relative to other nucleic acids present in the sample. Instead, non-specific amplification increases the absolute amount of all nucleic acids present in the reaction mixture.

49. Second, specific amplification methods commonly achieve ***exponential*** amplification of the target sequence, as compared with linear amplification. Sustained, significant, exponential amplification is a hallmark of specific amplification methods. In contrast, the non-specific amplification methods described in the '338 patent achieve only linear amplification, not exponential amplification. For example, because random primers bind at various places along the nucleic acids present in the sample, the products of amplification are generally fragmented and may or may not include the sequence to be detected. If these products were then subjected to another round of non-specific amplification, the resulting products would be smaller still. Multiple rounds of non-specific amplification thus diminish rapidly in efficiency, whereas multiple rounds of specific amplification produce extraordinarily large amounts of the isolated full size product nucleic acids in very short periods of time.

50. Third, non-specific amplification using random hexamer primers results in fragmented nucleic acids, each of which contains the random sequences present in the random primers. The resulting products are thus heterogeneous and have undefined composition. Such nucleic acids are unsuitable for most of the purposes for which homogeneous, specifically amplified nucleic acids of known composition are employed. As a result, Gen-Probe's TMA method also does not yield the same result as that obtained with non-specific amplification.

51. The inventors and other employees of Gene-Trak/Vysis admitted that the non-specific methods of amplification disclosed in the specification of the '338 patent were "different" from specific amplification methods and further admitted that non-specific amplification was the "opposite" of specific amplification methods such as TMA. The text of the '338 patent specification itself admits and highlights the differences between the two methods of amplification.

E. THE '338 PATENT IS INVALID

52. The claims of the '338 patent are invalid by reason of one or more provisions of Title 35 of the United States Code.

1. Lack of Enablement Under 35 U.S.C. §112, ¶1

53. Vysis contends that the relevant disclosure for the '338 patent was filed on December 21, 1987. In the specification, the inventors disclosed three preferred embodiments, Examples 1 through 3, that show *only* the use of target capture without amplification. In the remaining four preferred embodiments, Examples 4 through 7, the inventors purport to disclose the combination of target capture followed by non-specific amplification techniques.

54. In Example 4, the inventors set forth an embodiment of their claimed methods that describes the use of *E. coli* RNA polymerase lacking sigma subunit, i.e., core enzyme. The sigma subunit is removed according to known procedures, but the '338 patent states that "other phage or bacterial RNA polymerases that lack transcriptional specificity can also be used." ('338 patent, col. 30:64-31:1.) The core enzyme is added to a nucleotide triphosphate/transcription buffer solution and the resulting non-specific transcription of the target DNA produces RNA transcripts of the target DNA, which are then captured using a capture probe that is homologous to a sequence of the RNA transcripts. The inventors describe the use of a reporter probe for detection. Example 4 describes a process that is known as "linear amplification."

55. In Example 5, the inventors describe the use of universal or random primers comprising random nucleotide sequences of short DNA fragments averaging about 6 nucleotides in length to prime or initiate DNA synthesis. These short sequences are known as "random hexamers" and their complementary sequences frequently occur within virtually all nucleic acids.

As a population, the random primers tend to hybridize at multiple points along any nucleic acid sequence even though each individual primer binds to its complementary sequence. In the presence of polymerase enzymes used to replicate and synthesize nucleic acids the binding of the random primers will initiate synthesis of complementary DNA sequences to form double-stranded DNA that in turn can be used as a template for the use of still further non-specific enzymes to make multiple copies (RNA transcripts) of any nucleic acids in the sample. In Example 5, the inventors describe the use of RNA polymerase lacking sigma subunit to make these transcripts. In a parenthetical statement in Example 5, the inventors say that a capture probe could be used to make the double-stranded DNA, followed by non-specific transcription. Example 5 describes, in all embodiments, a linear, non-specific amplification process.

56. Vysis has admitted during discovery that it never attempted to practice the methods described in Examples 4 and 5. Vysis never actually reduced to practice the inventions described in Examples 4 and 5. Significant information that would be needed to enable one skilled in the art to practice linear amplification is omitted from Examples 4 and 5. The linear, non-specific amplification methods of Examples 4 and 5 are not enabled by the disclosures of the '338 patent's specification.

57. Amplification methods may be linear or exponential. Exponential amplification is entirely different from linear amplification. Exponential amplification can be thought of as a process of making copies of copies, *i.e.* the amplification products themselves are further amplified, resulting in a geometric increase in the amount of the products. In contrast, linear amplification can be described as making one copy at a time from the same original template. Linear amplification differs substantially from exponential amplification in that in linear amplification techniques copies are not made from copies. Rather, copies are only made individually from the original target nucleic acid sequences, or a double-stranded template made from the target nucleic acid. Thus, after one cycle you have one copy, after two cycles, you will have two copies, and so on.

58. One of the significant advancements in molecular biology was the invention of the polymerase chain reaction ("PCR") method of nucleic acid amplification. This method permitted

exponential amplification of a specific target sequence. Following the announcement of the PCR method in 1985, those skilled in the art distinguished between linear amplification and exponential amplification methods. TMA is an exponential amplification method.

59. One of ordinary skill in the art would not only recognize the substantial differences in the function and way that exponential techniques work when compared to linear techniques, but one of ordinary skill would also recognize that substantial differences exist in the result and utility of the two techniques. The linear amplification techniques would require more "target" to be present in a sample as well as more time to have a reasonable chance of ultimately being able to detect or measure any amplification products above background levels. Exponential amplification is substantially different. Exponential amplification requires much less target to be present in the sample (i.e., because even one instance of the target can rapidly be multiplied) and less time to yield sufficient copies to permit detecting/measuring the amplification products above background levels. For this reason, exponential amplification is much more suitable for use in diagnostic applications because it results in more copies of the target nucleotide being made available over the same time. Thus, in a diagnostic application, a scientist can begin with much less target material and spend less time to produce an appropriate level of target for detection. This makes exponential amplification far more practical for use in diagnostics than linear amplification. Methods of linear amplification did not offer the advantages of exponential amplification and could not compete with PCR or TMA for routine use in amplified clinical assays.

60. The claims of the '338 patent encompass both non-specific linear and non-specific exponential amplification. Examples 4 and 5 purport to describe methods of linear amplification only. Neither Example 4 or 5 describe a method by which exponential amplification of the target polynucleotide can be achieved. Hence, Examples 4 and 5 are not enabling of the invention as broadly as it is claimed.

61. In Example 6, the inventors set forth an embodiment of their claimed methods that describes the use of "random" primers and cycles of heating. The patent does not state whether the exemplified process is linear or exponential; however, Vysis has belatedly asserted that the process of Example 6 will allow exponential amplification of a target DNA sequence. As the specification

provides, the random primers are six-base oligonucleotides constructed such that the bases at each nucleotide position are constructed in random sequence. As a matter of statistical variation, some of the random primers can be expected to bind to any polynucleotide present in a sample. Following that non-specific binding, a standard DNA polymerase, Klenow fragment, is then used to form double-stranded DNA from the original polynucleotide. The double-stranded DNA is then heated resulting in a physical separation of the double-stranded DNA into its two complementary single strands of DNA (i.e., the original strand and its complementary strand). Once separated into two strands, the process of creating doubled-stranded DNA from each single strand is repeated about 10 times using random primers and additional DNA polymerase. According to the '338 patent, the process would result in 1000-fold increase in the level of target DNA. (Col. 32, lines 2-5.)

62. In Example 7, the inventors described the apparent use of a natural enzyme, Qß replicase, to nonspecifically amplify target RNA. According to this example, transcripts or alternatively, ribosomal RNA ("rRNA"), are first captured, and then RNA complementary to the captured RNA is synthesized. The specification then states that the Qß replicase enzyme could be used to make copies of the target RNA exponentially. However, the specification does not provide any detail as to the method by which one would accomplish that technique. Rather, it merely suggests that the procedure disclosed in a paper authored by Thomas Blumenthal in 1980 would allow the claimed exponential amplification of the target polynucleotides.

a. Example 6 was never successfully practiced by Vysis or its predecessor, Gene-Trak.

63. To the extent that the inventors' disclosure of Example 6 in prophetic format suggests that they had not attempted to reduce that technique to practice by the filing date of December 21, 1987, Gene Trak's internal records show otherwise. To the contrary, Gene Trak's internal records show that Gene Trak's designated "amplification group" undertook a dedicated project with the express object to successfully implement nucleic acid amplification using random primers.

64. Gene Trak's amplification group initiated that project in July 1987. That group was

staffed by skilled scientists who reported directly and indirectly to senior scientists and managers at Gene Trak, including Jonathan Lawrie, one of the named inventors of the '338 patent. One of the amplification group's stated goals was to reduce to practice the technique for non-specific amplification using random primers as set forth in Example 6.

65. Using more elaborate experimental details and techniques than those disclosed in Example 6, Gene Trak's amplification group struggled for at least 5 months attempting to non-specifically amplify a target nucleic acid with random primers. They never succeeded. Indeed, rather than *amplify* the target, the results of their efforts resulted in a *net reduction* in target. Eventually, the amplification group at Gene Trak abandoned their efforts.

66. In their unsuccessful effort to reduce the technique disclosed in Example 6 to practice, Gene Trak's team made a number of observations that bear upon the issue of enablement. Most significantly, they concluded that amplification using random primers was "impractical for exploitation as an amplification scheme," and "of limited use for target amplification." Second, they also found that the technique was also "very sensitive to perturbation, that is, changes in experimental condition such as primer concentration."

67. Neither Gene-Trak nor Vysis ever successfully performed the technique disclosed in Example 6. Thus, the method of Example 6 was never actually reduced to practice.

68. Gene Trak's failure to practice the technique of Example 6 was predictable and inevitable. As Gene Trak's team discovered, *any* technique using non-specific amplification with random primers is subject to significant perturbation which therefore requires an inordinate amount of experimentation to implement—the details of which are not disclosed in the specification.

69. The experimental details required to practice non-specific amplification methods using random primers was separately patented in August 1991 by James Hartley and later in April 1992 by Dr. Hartley and another scientist, Mark S. Berninger. The details disclosed in their patents, United States Patent Nos. 5,043,272 and 5,106,727, respectively, dramatically contrast the experimental details necessary to practice random priming amplification with the limited disclosures of the specification of the '338 patent.

70. As Gene Trak's investigators discovered, the technique for random priming amplification requires extensive work to determine the reaction conditions and parameters that will allow amplification to occur. The details of these conditions are missing from the '338 patent disclosure. For instance, Example 6 purports to use a particular DNA polymerase, Klenow fragment, but Example 6 does not specify the amount of this enzyme that should be used. Furthermore, the concentration of primers and the incubation times and temperatures for DNA synthesis are also not disclosed in Example 6. Similarly, although Example 6 purports to use certain reactants such as deoxynuclotide triphosphates ("dNTP's") as part of the reaction, Example 6 does not specify the amount of these components. Furthermore, Example 6 directs the use of "appropriate buffer," but does not specify the components or concentration to be used.[3]

71. The experimental parameters for each of the foregoing conditions and components for random primer amplification are critical to the successful practice of amplification using random primers. As evidenced by the unsuccessful efforts of Gene Trak, as of December 21, 1987, one of ordinary skill in nucleic acid amplification would not have been able to determine the necessary parameters and techniques for random priming amplification from Example 6 without undue and significant experimentation. Indeed, as of the filing date, there was no published data or technique that would even suggest that *any* technique for amplification using random primers could succeed or any basis to believe that the skeletal details provided in Example 6 would enable exponential amplification of a target nucleic acid.

b. Neither Gene Trak nor Vysis ever attempted the technique disclosed in Example 7.

72. Example 7 purports to describe non-specific amplification of target nucleic acids using an RNA polymerase known as Qß replicase. With the limited disclosure of Example 7, the inventors claimed that one could obtain exponential amplification of any target nucleic acid.

73. Qß replicase is a naturally occurring enzyme that is derived from bacteria infected

[3] With respect to the buffer prescribed for use in Example 6, it is not at all clear what the composition and concentrations the inventors intended. Even if one were to assume that the buffer described in Example 5 were to be used, however, the disclosure of the buffer described in Example 5 lacks still further information concerning the concentration of Klenow polymerase, the concentration of hexamer primers, and the times and temperature of incubation.

by a virus known as Qß. As of 1987, Qß replicase was known to have extraordinary specificity that prevented it from copying nucleic acids other than Qß genomic RNA. In other words, the Qß replicase enzyme will not naturally copy or amplify target nucleic acids other than the specific sequence of Qß genomic RNA.

74. Contrasted with the extensive, albeit unsuccessful, efforts of Gene Trak scientists to practice Example 6, as of the filing date of the '338 patent, Gene Trak scientists never attempted to implement the technique of Example 7. To this date, neither Gene Trak nor Vysis scientists have ever attempted to perform the technique disclosed in Example 7. Thus, the method of Example 7 was never actually reduced to practice.

c. The Disclosure of Example 7 is also deficient.

75. The likely reason for Gene Trak's failure to attempt Example 7 is directly attributable to the absence of any disclosure of the experimental details necessary to obtain non-specific amplification of target nucleic acids with Qß replicase. The full extent of the disclosure provided in Example 7 is the suggestion to follow a procedure set forth in a 1980 publication by Thomas Blumenthal.

76. At best, in 1980, Thomas Blumenthal published the results of experiments in which he obtained fragmentary, partial transcription copies of 3 synthetic and 2 naturally occurring RNA molecules. He reported that he obtained that success through extensive experimentation that resulted in wide variances between the reaction conditions necessary to transcribe each of the target RNAs. Significantly, his results showed that the reaction conditions for each different target nucleic acid differed appreciably and, most importantly, unpredictably for each different target nucleic acid. As such, a mere reference to Blumenthal's paper would not provide sufficient detail to enable skilled scientists to amplify any given target nucleic acid without undue experimentation.

77. Another equally significant problem with the reliance on Blumenthal's study lies in the fact that it only attempted to obtain a single, complementary transcript copy of each target nucleic acid. Upon conclusion of the reaction described by Blumenthal, the complementary transcript copy of the target RNA remains coupled to the target thereby rendering both the target and the complementary copy unavailable for further copying by Qß. The entire process results in

the creation of only one additional complementary nucleic acid for each target molecule. Thus, even if a complementary transcript copy was successfully synthesized, the Blumenthal technique results in a termination of the reaction upon creation of that complementary transcript. Such a result – the creation of a single complementary copy per target molecule is not "amplification" of the target.

78. Moreover, Example 7 of the '338 patent purports to teach a method of *exponential* amplification of target nucleic acids using Qß replicase whereby template products are created and used to make still further amplified target molecules. Blumenthal's paper only showed limited success in the linear production of fragmentary portions of a few selected nucleic acids. As of 1987, not even Blumenthal had achieved success in using Qß replicase to obtain the claimed exponential amplification of target molecules. Thus, in 1987, no methods were known in which Qß replicase could be used to exponentially amplify target nucleic acids.

79. Accordingly, the evidence of "enablement" of Example 7 is equally lacking. There was no scientific knowledge in 1987 that would allow a person of ordinary skill to perform exponential target amplification using the enzyme Qß replicase. The minimal disclosure of Example 7 certainly did not provide the missing information. Even as to linear amplification using Qß replicase, the only evidence supporting that technique showed that the conditions necessary to transcribe fragments of selected target nucleic acids varied unpredictably, thus requiring an extraordinary amount of experimentation to achieve if at all possible.

80. Thus, in each of the two preferred embodiments claimed to disclose exponential non-specific amplification, Examples 6 and 7, Gene Trak did not and could not enable either linear or exponential amplification using the techniques disclosed in those embodiments. Examples 4 and 5 disclose only linear amplification, and they, too, were never actually reduced to practice.

2. Obviousness, Anticipation, and Prior Public Disclosure Under 35 U.S.C. §§102, 103

a. The priority date of the '338 patent is no earlier than January 31, 1991.

81. Vysis asserts that the claims of the '338 patent are entitled to a December 1987 priority date. However, for a multiple of prosecution irregularities committed by Vysis and its

predecessors in the prosecution of the '338 patent, Vysis is not entitled to that claimed priority date.

82. On October 23, 1986, the applicants filed a patent application entitled "Target and Background Capture Methods and Apparatus for Affinity Assays." After filing, the Patent Office assigned that application the numerical designation, Serial No. 06/922,155 (the "'155 application"). Although, the '155 application purported to describe a technique for reversible target capture, it contained no disclosure of or claims to amplification techniques as claimed by Vysis in the '338 patent. The application identified Mark L. Collins as the sole inventor of the alleged inventions claimed in the '155 application.

83. On December 21, 1987, prior to substantive examination of the '155 application by the Patent Office, Vysis filed a Continuation-in-Part of the '155 application. The Patent Office assigned this Continuation-in-Part application Serial No. 07/136,920 (the "'920 application"). The applicants entitled the '920 application "Target and Background Capture Methods with Amplification," and initially submitted claims in the '920 application to methods of nucleic acid capture and amplification (claims 1-23), and a claim to an instrument for performing assays for target polynucleotides (claim 24).

84. In its initial examination of the '920 application, the Patent Office issued a restriction requirement because it deemed the claimed inventions of capture and amplification claims and the instrument claims of the '920 application as distinct. In response to that restriction requirement, the applicants elected to proceed in the '920 application by prosecuting only the method claims (claims 1-23).

85. On July 20, 1990, following the applicants' election to proceed with only the method claims in the '920 application, the Patent Office issued an office action regarding that application by which it rejected all claims of the '920 application on prior art and other grounds of patentability. The Patent Office provided the applicants until October 20, 1990, with extensions available until January 20, 1991, to submit a substantive response to that office action.

86. Rather than prepare a substantive response to the July 20, 1990 office action, and in order to continue prosecuting claims to methods of nucleic acid capture and amplification, on

January 22, 1991, the applicants filed a continuation application from the '920 application. The Patent Office designated this continuation application as application Serial No. 07/644,967 (the "'967 application"). The '920 application became abandoned as of midnight, January 22, 1991 pursuant to 35 U.S.C. § 133.

87. On March 12, 1991, the Patent Office issued an office action for the '967 application by which it issued a final rejection of all claims in that application. Pursuant to statute, the Patent Office provided the applicants with a shortened response period until June 12, 1992 to respond to this final rejection of the claims of the '967 application.

88. The '967 application became abandoned as of midnight, June 12, 1992 pursuant to 35 U.S.C. § 133. On September 24, 1992, Vysis filed a petition to revive the '967 application through September 14, 1992, the date to which it could have automatically obtained an extension of time by paying a fee. The PTO granted Vysis's petition to revive the '967 so that it would become abandoned as of midnight, September 14, 1992 (rather than remain abandoned as of midnight June 12, 1992).

89. Rather than prepare a substantive response to the March 12, 1992, office action, and in order to continue prosecuting claims to methods of nucleic acid capture and amplification, on September 14, 1992, the applicants filed a continuation application to the '967 application. (At that time the prior '967 application was abandoned, but it was revived as set forth above.) The Patent Office designated this further continuation application Serial No. 07/944,505 (the " '505 application"). Consistent with continuation practice and rules, the applicants presented only claims to methods of nucleic acid capture and amplification in the '505 application, the instrument-related claim having been withdrawn by prior election.

90. The '505 application became abandoned as of midnight, February 5, 1993 pursuant to 35 U.S.C. § 133. Following the PTO's rejection of all claims in the '505 application, Vysis took no action with respect to the '505 application for approximately one year and six months, until May 3, 1994.

91. On November 5, 1992, the Patent Office issued an office action for the '505 application by which it issued a final rejection of the claims submitted with that application.

Pursuant to statute, the Patent Office provided the applicants with a shortened response period until February 5, 1993 to respond to this final rejection of the claims of the '505 application. Applicants' counsel received this office action and his staff docketed the deadlines for response.

92. With the applicants' express knowledge and awareness of the requirement to respond to the November 5, 1992 office action within the statutorily required time and the further knowledge of the consequences of abandonment arising from any failure to respond within that required time, applicants intentionally elected not to respond to the office action.

93. Consistent with Patent Office rules and procedures, following the applicants' failure to respond to the November 5, 1992 office action, on June 16, 1993, the Patent Office sent a formal notice of abandonment of the '505 application to the applicants. Applicants' counsel received this notice of abandonment and his staff docketed the deadlines for response. However, consistent with the applicants' intentional decision not to respond to the office action, the applicants intentionally determined not to respond to the notice of abandonment.

3. Facts Related to the Prosecution of the Alleged Instrument Invention

94. The applicants intentionally failed to respond to the November 5, 1992, office action rejecting the claims of the '505 application and further intentionally failed to respond to the June 16, 1993 notice of abandonment as a result of their decision to abandon the alleged invention directed to methods of nucleic acid capture and amplification originally elected for prosecution in the '920, '967 and '505 applications.

95. On January 31, 1991, consistent with the applicants' decision to acquiesce to the Patent Office's July 20, 1990 restriction requirement issued with respect to the distinct claimed inventions that applicants presented in the '920 application, the applicants filed a separate application by which they elected to prosecute only instrument-related claims. The Patent Office assigned this instrument application Serial No. 07/648,468 (the "'468 application"). As originally filed (and consistent with their election in response to the restriction requirement imposed in the '920 application), the applicants submitted only claims directed to an instrument for performing assays for target polynucleotides. The applicants entitled the '468 application "Closed Vessel for Isolating Target Molecules and for Performing Amplification." The '468 application claimed four

inventors, only one of whom was an inventor on the '967 application. From the time of its filing in January 1991 until July 1, 1999, the '468 application directly claimed the benefit of the filing date of the '920 application.

96. Through the '468 application, the applicants claimed priority of their instrument invention as a continuation-in-part application to the '920 and earlier '155 applications. This claim of priority resulted from the deliberate and intentional choice of counsel for the applicants. However, applicants' claim to priority to the '920 and '155 applications was defective under 35 U.S.C. § 120 for several reasons.

97. First, in order to claim priority to a prior application, at least three requirements must be met: 1) there must be co-pendency with the prior application; (2) there must be continuity of invention and 3) there must be at least one inventor of common subject matter between the two inventions.

98. The element of co-pendency required that the '468 application have been filed prior to the abandonment of the priority applications. In this case, although the applicants filed the '468 application on January 31, 1991, they had intentionally abandoned the '920 application on January 22, 1991 and intentionally abandoned the '155 application on February 3, 1990. Applicants and their counsel intentionally failed to disclose this lack of co-pendency of the '468 application during the prosecution of the '468 application. Due to the lack of co-pendency, the earliest date to which the '468 patent could claim priority under Section 120 was its own filing date of January 31, 1991. (As of this date, a PCT counterpart application to the applications for the method ultimately disclosed '338 patent had already been published and such publication established a statutory bar to any claims in the United States for similar inventions.)

99. Even ignoring the defective claim of co-pendency, the requirement of Section 120 for a common inventor provides continuity only as to that subject matter contributed by the common inventor. In this case, the only common inventor was Mark Collins. In deposition testimony in this case, Dr. Collins admitted that his sole contribution to the '920 application (and the '338 patent) related to the process of target capture (as embodied in steps (a) and (b) of Claim 1 of the '338 patent). Thus, at most, the only subject matter that was "carried forward" into the

'468 application was the concept of target capture to the extent embodied in the disclosure and claims of the '468 application.

100. In their claim of priority to the '920 and '155 applications, the applicants did not disclose the limited nature of the contribution provided by Mark Collins to the inventions claimed therein. Although that lack of disclosure may not have been material to the prosecution of the '468 application per se, it is extremely relevant to later stages of the prosecution of the '338 patent.

101. The Patent Office initially rejected all the claims of the '468 application on prior art and other grounds of patentability in an office action mailed March 18, 1992. The Patent Office provided the applicants until June 18, 1992 to submit a substantive response to that office action.

102. Rather than prepare a substantive response to the March 18, 1992 office action, and in order to continue prosecuting claims to an instrument for performing assays for target polynucleotides, on September 17, 1992, the applicants filed a continuation application from the '468 application. The Patent Office designated this continuation application as application Serial No. 07/946,749 (the "'749 application"). Consistent with the restriction requirement originally issued in the '920 application, the applicants submitted only claims directed to an instrument for performing assays for target polynucleotides in the '749 application. The '468 application was abandoned as of midnight, September 18, 1992.

103. The Patent Office initially rejected all the claims of the '749 application on prior art and other grounds of patentability in an office action mailed March 22, 1993. The Patent Office provided the applicants until June 22, 1993 to submit a substantive response to that office action. In rejecting the '749 application, the PTO recognized that:

> the present application does not receive benefit of the filing date of 06/922155 and 07/136920. The prior applications, 06/922155 and 07/136920, fail to disclose or suggest the present invention. The continuity between the present application and the other appear only to be in the area of amplification rather than in the scope of the invention. The present application is therefore believed to only have benefit of the filing date, 1/31/1991, of 07/648468.

(March 22, 1993 office action at page 2, lines 1-10.

104. Rather than prepare a substantive response to the March 22, 1993 office action, and in order to continue prosecuting claims to an instrument for performing assays for target

polynucleotides, on September 21, 1993, the applicants filed a continuation application from the '749 application. The Patent Office designated this continuation application as application Serial No. 08/124,826 (the "'826 application"). Consistent with the restriction requirement originally issued in the '920 application, the applicants submitted only claims directed to an instrument for performing assays for target polynucleotides in the '826 application. The '749 application was abandoned as of midnight, September 22, 1993.

105. The Patent Office initially and finally rejected all the claims of the '826 application on prior art and other grounds of patentability in an office action mailed December 9, 1993. The Patent Office provided the applicants until March 9, 1994 to submit a substantive response to that office action. In rejecting the '826 application, the PTO recognized that the application did not receive the benefit of the filing date of the '155 and '920 applications because those prior applications failed to disclose or suggest the invention claimed in the '468, 749, and '826 applications.

106. Rather than prepare a substantive response to the December 9, 1993 office action, and in order to continue prosecuting claims to an instrument for performing assays for target polynucleotides, on June 8, 1994, the applicants filed a continuation application from the '826 application. The Patent Office designated this continuation application as application Serial No. 08/257,469 (the "'469 application"). Consistent with the restriction requirement originally issued in the '920 application, the applicants submitted only claims directed to an instrument for performing assays for target polynucleotides in the '469 application. The '826 application was abandoned as of midnight, June 9, 1994.

107. The Patent Office initially and finally rejected all the claims of the '469 application on prior art and other grounds of patentability in an office action mailed September 12, 1994. The Patent Office provided the applicants until December 12, 1994 to submit a substantive response to that office action. In rejecting the '469 application, the PTO recognized that the application did not receive the benefit of the filing date of the '155 and '920 applications because those prior applications failed to disclose or suggest the invention claimed in the '468, 749, '826, and '469 applications.

108. Rather than prepare a substantive response to the December 12, 1994 office action, and in order to continue prosecuting claims to an instrument for performing assays for target polynucleotides, on March 8, 1995, the applicants filed a continuation application from the '469 application. The Patent Office designated this continuation application as application Serial No. 08/400,657 (the "'657 application"). Consistent with the restriction requirement originally issued in the '920 application, the applicants submitted only claims directed to an instrument for performing assays for target polynucleotides in the '657 application. The '469 application was abandoned as of midnight, March 13, 1995.

109. The Patent Office initially and finally rejected all the claims of the '657 application on prior art and other grounds of patentability in an office action mailed April 25, 1995. The Patent Office provided the applicants until July 5, 1995 to submit a substantive response to that office action. In rejecting the '657 application, the PTO recognized that the application did not receive the benefit of the filing date of the '155 and '920 applications because those prior applications failed to disclose or suggest the invention claimed in the '468, 749, '826, '469, and '657 applications.

110. Rather than prepare a substantive response to the April 25, 1995 office action, on October 25, 1995, the applicants submitted a notice of appeal of the '657 application. Rather than file an appeal brief, and in order to continue prosecuting claims to an instrument for performing assays for target polynucleotides, on March 25, 1996, the applicants filed a continuation application from the '657 application. The Patent Office designated this continuation application as application Serial No. 08/622,491 (the " '491 application"). Consistent with the restriction requirement originally issued in the '920 application, the applicants submitted only claims directed to an instrument for performing assays for target polynucleotides in the '491 application. The '657 application was abandoned as of midnight, March 25, 1996.

4. Applicants' Efforts to Overcome their Intentional Abandonment of the '505 Application and their Alleged Claims to Methods of Nucleic Acid Capture and Amplification

111. Sometime prior to May 3, 1994, the applicants determined to attempt to reverse their prior intentional abandonment of the alleged invention directed to methods of nucleic acid

capture and amplification. As a result of that determination, on May 3, 1994, fifteen months after they failed to respond to the office action of November 5, 1993 and almost eleven months after they further failed to respond to the formal notice of abandonment, applicants attempted to revive their '505 application by filing a formal petition to revive the '505 application. In that petition, the applicants misrepresented the fact concerning their prior intentional abandonment of the '505 application and claimed that they "unintentionally" failed to respond to the Patent Office. The applicants stated that "[t]he abandonment occurred as a result of the oversight of Applicants representative and was not intended by Applicants."

112. As set forth above, the applicants' claim of unintentional abandonment of the '505 was false. Rather, the applicants' failure to respond to the Patent Office's rejection of the claims of '505 application directed to the claimed invention of a method of nuclei acid amplification was intentional. Indeed, the applicants' intentional decision not to respond to the '505 office action was consistent with and driven by applicants' underlying decision to abandon the invention claimed in the '505 application.

113. On October 27, 1994, the Patent Office rendered a decision denying the applicants' petition to revive the '505 application. As the Patent Office explained, the '505 application became abandoned on February 6, 1993, when the applicants failed to respond to the office action of November 5, 1992. Because the petition to revive the '505 application was filed more than one year after the '505 application became abandoned, the petition was barred under 37 C.F.R. 1.137(b). Accordingly, the Patent Office refused to revive the '505 application under 37 C.F.R. 1.137(b).

114. The Patent Office informed the applicants that they might be able to revive the '505 application under the provisions of 37 C.F.R. 1.137(a). However, the Patent Office explained that "in view of the fact that this case has been abandoned for an inordinate period of time, petitioner must show diligence between the time of becoming aware of the abandonment of the above-identified application and the filing of a petition to revive."

115. The applicants declined to seek relief pursuant to 37 C.F.R. 1.137(a), thereby acquiescing to the Patent Office's determination that the '505 patent was abandoned on February

6, 1993.

116. Concurrent with their ultimately unsuccessful effort to revive the '505 application, on May 3, 1994, the applicants filed a new original application that the Patent Office designated as Serial No. 08/238,080 (the "'080 application"). In the '080 application, the applicants did not initially disclose to the Patent Office that the application was virtually identical to one that they intentionally abandoned in the '505 application or of the fact of that abandonment. In addition, the applicants also failed initially to disclose the fact of their concurrent efforts to revive the '505 application. Furthermore, notwithstanding the fact that the applicants knew and intended that the '080 application should be treated as a new original application, applicants did not submit new oaths from the alleged inventors for the '080 application. The applicants also failed to disclose to the Patent Office that, as an original application, the claims of the '080 application were anticipated by the prior publication on August 23, 1989, of the applicants' own European application corresponding to the '920 application, European Application No. 88312135.2 (EP 0328829).

117. As a result of the applicants' intention to treat the '080 application as an original application and their concurrent failure to submit new oaths to support that application, on June 3, 1994, the Patent Office issued a notice to the applicants by which the Patent Office indicated that it had noted that the applicants had failed to file proper oaths or declarations for the '080 application.

118. In response to the Patent Office's notice to file the missing oaths necessary to support the '080 application, on July 5, 1994, the applicants submitted a formal response to that notice by which response the applicants first disclosed the prior abandonment of the '505 application and petitioned the Patent Office to consider the '080 application as a continuation application to the abandoned '505 application. The applicants' concurrently petitioned the Patent Office to consider the '080 application as filed under 37 C.F.R. § 1.60 as a continuation of their previously-abandoned '505 application. However, through this response and the petition incorporated therein, the applicants continued to misrepresent the prior abandonment of the '505 application and invention as "unintentional."

119. On October 27, 1994, the Patent Office formally dismissed the applicants' petition

to revive the '505 application. As of October 27, 1994, when the petition to revive the '505 applications was denied, the effective filing date for the '080 patent was its own filing date, May 3, 1994.

120. The applicants did not disclose the decision denying the petition to revive the '505 application to the branch of the Patent Office handling the applicants' petition in the '080 application to treat the '080 application as a continuation application to the '505 application. In any event, however, on March 14, 1995, the Patent Office formally dismissed that petition as moot and declared that the '080 application would be processed with a filing date of May 3, 1994.

121. The Patent Office decisions denying the applicants' petitions to revive the '505 application and to treat the '080 application as a continuation of the '505 created significant, indeed insurmountable, impediments to the applicants' desire to recant and reverse their earlier abandonment of the '505 application and the alleged invention comprising the amplification methods presented therein. Among other problems raised by those decisions, the applicants knew that unless they could manipulate the priority claim for the '080 application, their own prior publications would constitute statutory bars to patentability.

5. Applicants' Efforts to Fraudulently Manufacture Claims of Priority for the '080 Application

122. In light of the foregoing fatal impediments to patentability of the method claims presented in the '080 application, the applicants then proceeded to manufacture a scheme to undermine the Patent Office decisions denying their ability to claim priority for the '080 application back through the '505 application. As the first step in that scheme, on December 5, 1995, the applicants submitted a preliminary amendment in the '080 application in which they claimed, for the first time, that the '080 application was a divisional application to the '657 application that the applicants filed on March 8, 1995 to pursue the instrument claims and invention first claimed in the '468 application. This claim of priority resulted from the deliberate and intentional choice of counsel for the applicants.

123. The applicants' efforts to change the claim of priority of the '080 application to the '657 application were improper for several reasons. First, as indicated above, the applicants had

previously elected to pursue only instrument-related claims in the '657 application (and earlier instrument-related applications). Second, the applicants' efforts to claim that the '080 application was a divisional application of the '657 application was additionally defective because the specification and claims of the '080 patent are different from and not supported by the specification and claims of the '657 application. Furthermore, the inventors on the '657 application were not the same as the inventors on the '080 application, and the '657 inventors could not have effectively disclosed the subject matter of the invention claimed in the '080 application.

124. However, in addition to the foregoing defects, the effort to claim priority for the '080 application also violated at least two fundamental requirements necessary to claim priority to the '657 chain of applications. First, as noted earlier, a claim of priority under Section 120 requires continuity of at least one inventor of common subject matter. (See discussion hereinabove.) In this case, applicants claimed that the '080 application met that requirement because Mark Collins was an inventor for the '657 application and also an inventor for the '080 application.

125. Yet, as noted above, Collins contribution to the '657 application was solely limited to the concept of target capture and did not include the concept of amplification. As such, the only subject matter, if any, common to both the '080 application and the '657 application was target capture. Because all of the claims of the '080 application require both target capture and amplification, the claims of the '080 application are not entitled to claim priority earlier than the filing date of the '080 application – May 3, 1994.

126. Vysis did not disclose the limited contribution of Mark Collins in its claim to priority through the '657 application and ultimately to the '920 application. The Patent Office would not have and did not otherwise discover that limited contribution prior to issuance of the '338 patent. In addition to the validity issues raised thereby, the failure to disclose that information constituted an independent act of inequitable conduct.

127. In addition, in applicants' zeal to implement their inequitable scheme to overcome the Patent Office determination that the claims of the '080 application were only entitled to claim

priority as of May 3, 1994, the applicants overlooked a further and equally significant defect in their effort to claim priority for the '080 application to the '657 application. Under the patent laws and regulations, an application is only entitled to claim priority to a prior application if such application was co-pending when the application claiming priority was first filed. Yet, with respect to the applicants' scheme to advance the priority of the '080 application, their claim to priority to the '657 application violated this requirement of co-pendency because the applicants did not file the '657 application until March 8, 1995, nearly one year ***after*** the applicants filed the '080 application! The applicants failed to advise the Patent Office of this lack of co-pendency in their December 5, 1995, preliminary amendment. The applicants knew, or should have known, that the representation that the '080 application was a divisional of the '657 application was improper, and that the applicants made this representation with the intent of deceiving and misleading the Patent Office.

6. The Request for Certificate of Correction Filed for the '338 Patent

128. The '338 patent issued from the '080 application on May 12, 1998. On December 14, 1998, the applicants submitted a Request for Certificate of Correction for the '338 patent.

129. Prior to filing the December 14, 1998, Request for Certificate of Correction for the '338 patent, the applicants identified two fatal defects in the claimed priority for the '338 patent, the first involving patent application Serial No. 07/648,468 and patent application Serial No. 07/136,920 and the second involving patent application Serial No. 08/238,080 and patent application Serial No. 08/400,657.

130. By the December 14, 1998, Request for Certificate of Correction, the applicants attempted to cure these fatal defects.

131. First, the applicants sought to change the claim of priority for the '080 application from a claim that it was a divisional of the '657 application to a claim that it was a continuation of the '826 application. (The '826 application had been pending when the '080 application was filed, but had already been abandoned when the Patent Office dismissed the applicants' petition to revive the '505 application.) This change was sought to avoid invalidity of the '338 patent.

132. Second, the applicants sought to change the claim of priority made for the '468

application from a claim that it was a continuation-in-part of the '920 application to a claim that it was a continuation-in-part of the '967 application. (The '920 application had already been abandoned when the '468 application was filed.) This change was sought to avoid invalidity of the '338 patent.

133. By the December 14, 1998, Request for Certificate of Correction the applicants attempted to cure fatal defects in the '338 patent by, among other things, representing to the Patent Office that the prior intentional choices made by patent counsel as to which "correction" was sought were "mistakes" and that those mistakes were of "minor character."

134. By the December 14, 1998, Request for Certificate of Correction the applicants attempted to cure fatal defects in the '338 patent by, among other things, representing to the Patent Office that the prior intentional choices made by patent counsel as to which "correction" was sought resulted from errors made in good faith by the applicants. The applicants knew that the true facts were that neither the request for Certificate of Correction nor any act after the abandonment of the '505 application was undertaken by applicants in good faith.

135. By the December 14, 1998, Request for Certificate of Correction, the applicants attempted to cure fatal defects in the '338 patent by, among other things, misrepresenting to the Patent Office the date of applicants' discovery of the mistakes for which correction was sought. The applicants knew that the true facts were that defects had been discovered earlier than they disclosed to the Patent Office.

136. By the December 14, 1998, Request for Certificate of Correction, the applicants attempted to cure fatal defects in the '338 patent by, among other things, representing to the Patent Office that the '505 application had been inadvertently and unintentionally abandoned. The applicants made this representation knowing that the true facts were that the '505 application was intentionally abandoned.

137. The applicants further represented in the Request for Certificate of Correction for the '338 patent that the '338 patent was a continuation of the '826 application. However, the '338 patent could not be a continuation of the '826 application, because the disclosure of the '338 patent was not identical to the disclosure of the '826 application. The applicants knew that the '338

patent could not be a continuation of the '826 application. As a direct result of the deceptive conduct of applicants set forth herein, the certificate of correction was entered by the Patent Office on September 7, 1999.

7. Applicants' Petition under 37 C.F.R. §1.182

138. On December 14, 1998, the applicants filed a petition with the Patent Office under 37 C.F.R. § 1.182 to amend the "specific references" and claims of priority stated in the '826, '749, and '468 applications so as to attempt to further cure one of the fatal defects in the priority claim for the '338 patent. At the time of such petition, however, the applicants had previously intentionally abandoned the '826, '749, and '468 applications and those applications had been abandoned for more than four years.

139. The applicants did not petition to revive the abandoned applications prior to seeking to make amendments. In order to overcome the impediment to its effort to cure the fatal defect in the claim of priority for the '338 patent arising in the '826, '749, and '468 applications, the applicants argued in its petition to amend the '826, '749, and '468 applications that an intentionally abandoned application could be amended after abandonment.

140. In petitioning to amend the three abandoned applications, applicants did not disclose to the PTO that they were seeking to circumvent applicants' abandonment of the '505 application nor did they even disclose the existence of that prior application.

141. As direct result of the deceptive conduct of applicants set forth herein, the petitions to amend the abandoned applications were granted by the PTO in a decision mailed July 1, 1999.

a. Even if the priority date of the '338 patent is December 21, 1987, isolation of target polynucleotides from a sample by capture on a solid support is disclosed in the prior art.

142. Even assuming the validity of Vysis' claimed December 21, 1987 priority date, third-party prior art exists that renders the '338 patent invalid under Sections 102 and 103. When scientists first began to undertake nucleic acid hybridization in the early 1960's, they quickly recognized that hybridization proceeded more efficiently if the target nucleic acid sequence was separated from other matter present in a sample or cellular extract. Several techniques were developed to accomplish such separation, such as density gradient centrifugation. The discovery

that single-stranded DNA strongly adhered to some solid supports, such as nitrocellulose membrane, made it possible to capture DNA on such a support for hybridization. Capture of a nucleic acid on a solid support, including nitrocellulose membranes, was described in numerous publications in the 1960's, including Gillespie, D. and Spiegelman, S. "A Quantitative Assay for DNA-RNA Hybrids with DNA immobilized on a Membrane," J. *Mol. Biol.* 12,829-842 (1965).

143. In 1975, E.M. Southern described a method whereby DNA fragments could be first separated and purified, transferred to a solid support (Southern transfer), and then identified by hybridization.

144. By 1985, scientists had improved capture methods using filters or membranes by the use of sandwich hybridization methods. In such methods, a nucleic acid sequence complementary to the target nucleic acid was affixed to a support, the target in solution was hybridized to the sequence fixed to the support, and a third labeled nucleic acid probe was hybridized to the target, thus forming the sandwich comprised of the fixed nucleic acid, the target nucleic acid, and the nucleic acid probe. Dunn, *et al.*, *Cell*, 12:23-36 (1977) (two-step sandwich hybridization assay); Syvanen *et al.*, *Nucleic Acids Res. 14*, 12:5037-5048 (1986) (one-step sandwich hybridization assay). These nucleic acid sandwich assays were analogous to earlier sandwich antibody-antigen assays (immunoassays) in which a solid support containing a bound capture antibody was used to capture a target antigen from a specimen and then a labeled antibody was bound to the captured antigen. The labeled antibody was often labeled with an enzyme that would amplify a signal due to the presence of the labeled antibody by its repeated production of a detectable product from a substrate for the enzyme in the assay. Both nucleic acid and antibody-based sandwich assays are assays in which a "ligand" binds to its "ligate."

145. The term "capture probe" in connection with hybridization assays refers to a nucleic acid sequence fixed (or capable of becoming fixed) to a solid support, where that sequence is complementary to the sequence of the target nucleic acid that is to be captured. Nucleic acid assays that relied on sandwich hybridization techniques were known before the filing date of the '338 patent as shown by the following references.

146. U.S. Patent No. 4,563,419 (Ranki, issued January 7, 1986) discloses a hybridization

assay in which target nucleic acid is isolated from a sample by hybridizing it to a complementary capture probe immobilized on a solid support (nitrocellulose filter) and separated from the sample by washing. The captured target polynucleotide is detected with a labeled probe.

147. Scientists also developed sandwich hybridization methods that did not rely on using nitrocellulose as the solid support. Polsky-Cynkin, *et al., Clin. Chem.* 31/9:1438-1443(1985) describe DNA hybridization assays in which target DNA is captured by a complementary probe affixed to a solid support. The solid supports employed included agarose beads (which are "retrievable" supports, as that term is defined in the '338 patent), polypropylene test tubes and polypropylene solid-phase receptacles (*e.g.*, see p. 1439). The captured target DNA on the solid support is separated from the sample and detected with a radiolabeled probe. Beads with magnetic, paramagnetic, and super paramagnetic properties were also used as retrievable solid supports, permitting the captured nucleic acid, bound to the support, to be easily removed from the sample. Advanced Magnetics Inc. (Cambridge, Massachusetts) was an early leader in the development and sale of such magnetic beads, and obtained patents for these inventions, including U.S. Patent No. 4,554,088 (Whitehead *et al.*, issued November 19, 1985) and U.S. Patent No. 4,672,040 (Josephson, issued June 9, 1987).

148. U.S. Patent No. 4,554,088 (Whitehead, issued November 19, 1985) discloses the use of single-stranded nucleic acid bound to dispersible magnetic beads to isolate complementary nucleic acid from a sample. The nucleic acid capture probe immobilized on a magnetic bead is employed as a "ligand" to bind its soluble "ligate", which is the complementary nucleic acid in the sample (see Table III, col. 17). The magnetic beads bound to target nucleic acid are magnetically separated from the sample and unbound (non-target) species are removed by washing (col. 17, 11. 36-40).

149. U.S. Patent No. 4,672,040 (Josephson, issued June 9, 1987) discloses isolating specific nucleic acid sequences from a sample by contacting capture probes immobilized on dispersible magnetic beads with a sample containing complementary target polynucleotides and separating the support and bound polynucleotides from the target. In particular, Josephson states:

Specific DNA or RNA fragments can also be isolated from genomic and cloned

> DNA by immobilization of a known probe to the magnetic particles and placing the coupled particles in contact with a mixture of nucleic acid fragments, including the desired species. After hybridization the particles may be magnetically separated from unbound materials, washed, and the hybridized molecules isolated. (Col. 19, 11.3-10).

Josephson further states that the magnetic particles can be used in binding assays (col. 16, 11. 13 *et seq.*).

b. Even if the priority date of the '338 patent is December 21, 1987, amplification of target polynucleotides, or target-like molecules, is disclosed in the prior art.

150. As of the filing date, scientists had developed and used a number of molecular biology techniques to make copies of a target polynucleotide or produce molecules (sometimes referred to as "reporter" molecules) by virtue of the presence of the target polynucleotide. These techniques included cloning, cell-free translation, and synthesis of cDNA from mRNA.

151. The specification of the '338 patent purports to disclose three types of *in vitro* amplification: non-specific transcription of DNA by *E. coli* RNA polymerase (Example 4); nonspecific enzymatic amplification of DNA by DNA polymerase primed by random hexamer primers with and without non-specific transcription (Examples 5 and 6); and non-specific amplification using Qß replicase enzyme (Example 7). To the extent that any of these methods might be used to replicate a target polynucleotide, they were each disclosed in the art prior to December 21, 1987. All of these methods would result in formation of a random and heterogeneous collection of fragments of any portion of the starting population of polynucleotides.

152. The use of *E. coli* RNA polymerase core enzyme to transcribe DNA into RNA *in vitro* was well known in the prior art, as acknowledged by the patentees in their citation in Example 4 to R. Burgess in *RNA Polymerase*, Cold Spring Harbor Press, pp. 69-100 (1976) ('338 patent, col. 30, 11. 62-64). In the absence of sigma protein, *E. coli* RNA polymerase initiates synthesis at any position in a DNA molecule. The use of random hexamer oligonucleotide primers to initiate non- specific enzymatic reproduction of polynucleotides was also known in the art, for example, as disclosed in Feinberg *et al., Anal. Biochem.* 132:6-13 (1983). It was well-known in the art that DNA polymerases required primers to initiate replication. To the extent that RNA sequences can be transcribed under certain conditions using the enzyme Qß replicase, patentees

have acknowledged that this is also known in the art by their citation of Blumenthal, *Proc. Natl. Acad. Sci. U.S.A.* 77:2601-2605 (1980) (at col. 32, 11. 16-17).

153. Besides the amplification methods described in the '338 Patent, other methods of making additional copies of a polynucleotide, or of a reporter molecule, were well known in the art before the filing date. For example, Gaubatz *et al., Biochim. Biophys. Acta* 825:175-187 (1985) had described a method of amplifying cDNA sequences by a DNA polymerase-mediated strand displacement synthesis.

154. Signal or probe amplification methods were developed in which the detection probe was labeled with enzymes that could amplify the signal generated when the detector probe bound to the target. For example, Kourilsky, *et al.*, (U.S. Patent No. 4,581,333, April 8, 1986) disclose the use of enzyme-labeled probes for use in diagnostic assays. The Kourilsky patent incorporates by reference the disclosures of Manning, *et al., Biochemistry* 16:1364 (1977) as a hybridization technique in which the enzyme-labeled probes may be employed. Manning, *et al.* employed target capture techniques to isolate rRNA genes.

155. Other signal amplification methods used the enzyme Qß replicase to make additional copies of the label affixed to the detector probe that had hybridized to the target. Such techniques were disclosed in Chu *et al., Nucleic Acids Research* 14(14):5591-5603 (1986) and the corresponding United States patent, which was filed before December 21, 1987 (U.S. Patent No. 4,957,858 (Chu *et al.*, September 18, 1990).

156. Moreover, the polymerase chain reaction ("PCR") method of target amplification using specific primers had been described in a number of publications before December 21, 1987 (*e.g.*, Mullis *et al., Cold Spring Harb. Symp. Quant. Biol,* LI:263-273 (1986); Saiki *et al., Nature* 324:163-166 (1986); Wong *et al., Nature* 330:384-386 (1987). Applications for United States patents for the PCR method were also filed before then, including U.S. Patent No. 4,683,202 (Mullis). The PCR method involves the use of specific primers to identify unique nucleic acid sequences of the target organism to be copied *in vitro* by a DNA polymerase. Thus, as of December 21, 1987, methods of amplifying a target polyneucleotide, or a reporter molecule based on the presence of the target polynucleotide, were well known to those skilled in the art.

c. Even if the priority date of the '338 patent is December 21, 1987, the combination of target capture on a solid support with amplification of the isolated polynucleotide is disclosed in the prior art, as is the motivation to combine target capture with amplification.

157. Following the discovery of reverse transcriptase in 1970, the development of DNA cloning in 1973, and DNA sequencing in 1975, methods were developed for detecting normal and mutant genes and for detecting and identifying infectious organisms in clinical samples. Almost all techniques used to study nucleic acids require that the nucleic acids be treated to remove or inactivate cellular components that rapidly degrade nucleic acids or that otherwise interfere with further manipulations. In addition, the low frequency of individual genes in the genome and/or the low concentration of individual gene expression products in soluble cellular components also require isolation and concentration of these nucleic acids from biological materials prior to further study. Therefore, scientists were motivated to develop methods to separate and/or concentrate individual genes from other cellular components, some of which could inhibit amplification or detection reactions. Many such procedures were known in the art prior to 1987, and it was easy and commonplace for scientists to combine various methods to isolate and concentrate particular nucleic acids from various biological materials. By combining multiple methods, scientists could obtain greater degrees of purity and concentration than could be achieved by a single method alone. In addition, scientists were motivated to produce copies of, or amplify, individual gene sequences to provide sufficient quantities for analysis and detection. Recombinant DNA cloning was one method that allowed scientists to isolate discrete DNA fragments from any organism and produce large amounts of the same DNA for further characterization. Although the desired nucleic acid can easily be made in abundance once it has been cloned, the initial DNA cloning itself is a laborious process. For example, starting from genomic DNA or DNA transcribed from unfractionated messenger RNA, a scientist usually had to screen many clones before finding one that contained the desired genetic sequence. *See, e.g.,* Maniatis *et al., Molecular Cloning A Laboratory Manual* (Cold Spring Harbor Laboratory, Cold Spring Harbor, NY 1982), pp. 309-362.

158. To increase the frequency of clones with a desired target sequence, scientists often isolated mRNA from tissue that specifically produced the target gene product because the absolute

and relative amounts of the desired target mRNA are greater. For example, mRNA was isolated from pancreatic islet cells to enrich for sequences encoding insulin. Methods were developed to separate mRNA from DNA, other RNAs, and to enrich the desired target and to remove cellular components that might interfere with the cloning process. Among the most commonly used methods was chromatography in which the poly(A) tail of mRNA hybridized to a complementary oligo(dT) on a solid support, i.e., target capture (see Maniatis *et al., supra*, Chapter 6). The isolated mRNA could then be converted to cDNA using reverse transcriptase, and the DNA was cloned and amplified by replication in bacterial cells. Thus, before the filing date, scientists routinely employed the combination of target capture and amplification to generate detectable amounts of nucleic acid sequences of interest.

159. Due, in part, to the laborious nature of amplification by cloning, scientists developed methods for *in vitro* amplification of nucleic acid sequences of interest, including those discussed above. Since scientists were aware that substances present in samples, *e.g.* polymerase inhibitors, could interfere with these methods of amplification, they were motivated to employ known target capture methods to purify the samples prior to *in vitro* amplification just as they had done for cloning, a process that includes steps carried out both *in vitro* and *in vivo* that may be adversely affected by impurities in the target nucleic acids.

160. Molecular biology techniques have been applied to the diagnosis of disease for decades. The sandwich assays discussed above, including both nucleic acid hybridization assays and immunoassays, have been used to detect infectious agents. Many sandwich assays employ a combination of target capture and amplification to enhance detection sensitivity. A representative sandwich assay of this type is disclosed, for example in U.S. Patent No. 4,925,785, which was filed on March 7, 1986 and issued on May 15, 1990. This reference describes an assay that employs capture of a target on a solid support and amplification of signal generation by using secondary probes.

161. Sandwich assays were used to capture the target upon a solid support prior to December 21, 1987 because scientists recognized that the presence of additional matter in the sample could interfere with the sensitivity of the assay (*e.g.*, by interfering with an enzyme used to

generate the amplified signal). Capture on a solid support was recognized as a means for reducing the inhibitory effects of these other components commonly found in a sample.

162. In some clinical samples, the number of infectious organisms present in the sample is small. To detect small numbers of target, the test sensitivity must be high. Diagnostic tests based solely on hybridization between complementary DNA sequences often lack sensitivity when the number of infectious agents in the sample is small because the signal over background that can be generated from a low number of hybrids is insufficient for reliable detection. Thus, scientists used amplification to enhance the signal obtained from the probe-target hybrids. For example, the probes were labeled with enzymes that would repeatedly transform a substrate into product to amplify the signal and enhance the sensitivity of detection. Alternatively, the microorganisms in the sample could be grown in culture before the hybridization assay was performed to increase the number of target organisms, and hence amplify the target sequences present in the sample tested.

163. Prior to December 21, 1987, one skilled in the art would have been motivated to combine technologies, such as nucleic acid hybridization, target capture, and amplification methods, to obtain the desired specificity and sensitivity in an assay that detects sequences of interest. An abundance of evidence indicates that the idea of capturing nucleic acids onto a solid support and enhancing detection of those nucleic acids by an amplification process was widely known by those skilled in the art prior to that date.

164. For example, prior to the filing date it was well known among those skilled in the art that a polynucleotide of interest could be purified from a sample by contacting it with a solid support that would bind the polynucleotide and then separating the bound target from the sample. Purification would remove components in the sample that would otherwise prevent or inhibit further manipulation (e.g., cloning or *in vitro* amplification) of the target polynucleotide.

165. One method commonly used to purify mRNA before the filing date involves contacting poly(A)-tailed mRNA in a biological sample with oligo(dT) bound to a solid support (e.g., cellulose) under conditions that permitted hybridization of the poly(A) tail with the oligo(dT) moiety (see Maniatis *et al., supra*, Chapter 6). After separating the support and bound mRNA from the sample, the purified mRNA could then be released from the solid support and used in a variety

of ways (e.g., in cDNA synthesis and/or molecular cloning). For example, Gaubatz *et al., Biochem. Biophys. Acta* 825:175-187 (1985) described the isolation of poly(A)+ mRNA using oligo(dT)-cellulose chromatography followed by conversion of the purified mRNA into cDNA and further amplification using the Klenow fragment of DNA polymerase.

166. Sequence-specific capture of a target polynucleotide was also well known in the art before December 1987. This could be accomplished by contacting a sample containing the target polynucleotide with a solid support and a capture probe that was capable of binding the solid support and that contained a sequence of nucleotides complementary to the target polynucleotide. For example, U.S. Patent No. 4,672,040 (Josephson) and U.S. Patent No. 4,554,088 (Whitehead, *et al.*) describe use of dispersible solid supports (magnetic beads) with bound polynucleotide capture probes for isolating target polynucleotides. By separating the magnetic beads with their adherent target polynucleotide, the target polynucleotide is separated from other sample components capable of inhibiting or negatively affecting further manipulation (*e.g.*, detection) of the target polynucletide.

167. Prior to the filing date of the '338 patent, the scientific literature had also taught that it would be useful to combine the techniques of target capture and amplification to enrich and detect target polynucleotides. For example, U.S. Patent No. 4,957,858 (Chu *et al.*) teaches an assay in which a reporter polynucleotide is amplified using the enzyme Qß replicase. The patent states that the assay method can be carried out on a raw specimen of biological material, but more typically is carried out on a sample processed "to remove materials that would interfere with detection" (see col. 7,11.7-15). The patent further describes a variety of known purification methods that can be used to isolate the target for the assay, including methods in which nucleic acid is "isolated from viriods, viruses or cells of a specimen and deposited on solid supports. . ." (see col. 7, 11. 18-54, particularly 11. 24-28).

168. Solid supports were widely used to isolate nucleic acids to study their structure and function or to detect the presence of a particular nucleic acid in a sample. Because the amount of a target polynucleotide in a sample is often very small, the desirability of increasing the proportional amount of isolated polynucleotide before further analysis or detection was obvious to one skilled

in the art. It was common practice in the art to capture small amounts of mRNA on solid supports, convert the mRNA to cDNA using reverse transcriptase, an RNA-dependent DNA polymerase, and then further amplify the cDNA by cloning prior to detecting and/or analyzing the DNA. Once methods of *in vitro* amplification became widely available, it was obvious to combine these techniques with target capture on solid supports. Moreover, because target capture was known to be less than 100% efficient, it would have been obvious to one skilled in the art to combine target capture with amplification procedures to increase the amount of captured target (i.e., to compensate for any losses during the capture step) before detection, particularly if the number of target molecules was, or might be, small.

169. The motivation of those skilled in the art to proceed in this manner was obvious in view of the benefit to be obtained. For example, the evidence will show that as of October 1986, Gen-Probe recognized the benefits of purifying a target for purposes of developing an effective assay.

170. This motivation was also described elsewhere. For example, in Brown *et al.*, "Methods of Gene Isolation" *Ann. Rev. Biochem.*, 43:667-693 (1974), the authors recognized the desirability of combining target capture on solid supports with amplification. The authors reviewed a number of methods for isolating nucleic acids of interest, and devoted one section to the use of polynucleotides fixed to insoluble matrices to isolate DNA. At pages 673-674, they describe using RNA or DNA fixed to an insoluble support to effect sequence-specific isolation of target DNA containing a sequence complementary to the probe. In their "Concluding Remarks" (page 687), Brown et al. state that purification of DNA (e.g., using polynucleotides fixed to insoluble matrices) could be coupled with a method by which, ". . . a small amount of a given gene can be increased enormously in amount" such as by an "amplification step. . . carried out *in vitro* by an efficient DNA polymerase, which would replicate faithfully each molecule of DNA many times."

171. Arsenyan *et al.*, *Gene* 11:97-108 (1980) also recognized the desirability of combining target capture with amplification. They described a method to produce "amplified homogeneous DNA sequences" for the purpose of studying gene arrangement. Their process captured complementary single strands of the 5S RNA gene by hybridization to probes affixed to

cellulose supports followed by elution of the captured strands, annealing of the strands to produce double stranded DNA which was inserted into a cloning vector, transformation of host cells with the vector, and amplification of the DNA by growing the transformed host cells. As of the filing date of the '338 Patent, it would have been obvious to one of ordinary skill in the art that other known amplification methods including those described above could have been substituted for the cloning method used by Arsenyan *et al.* The obviousness of such substitution is suggested by the patentees' broad definition of "amplify" in the '338 Patent (col. 2, lines 9-19). Substituting other methods of amplification for amplification by cloning would have been obvious to one skilled in the art by December 1987.

172. For example, Gaubatz *et al., Biochem. Biophys. Acta* 825:175-187 (1985) described the isolation of mRNA by using oligo(dT)-cellulose chromatography followed by conversion of the purified mRNA into cDNA and amplification of the cDNA using polymerase-mediated strand displacement procedure. Powell *et al.*, Cell 50:831-840 (1987) described isolating poly(A) + RNA by oligo(dT)-cellulose chromatography to capture mRNAs of interest, followed by synthesis of cDNA and PCR amplification of the cDNA and detection of specific sequences of interest.

173. Two additional references show that purification of a target nucleic acid on a solid support (i.e., chromatography) and amplification of the target *in vitro* by using the enzyme Qß replicase was known before the filing date: Feix *et al.* "Replication of Viral RNA, XVI. Enzymatic synthesis of infectious viral RNA with noninfectious Qß minus strands as template," *Proc. Natl. Acad. Sci. USA* 59 (1): 145-152 (1968), and Pollet *et al.*, 1967, "Replication of Viral RNA, XV. Purification and properties of Qß minus strands," *Proc. Natl. Acad. Sci. USA* 58 (2): 766- 773 (1967). Feix *et al.*, 1968, disclose (1) purification of a target RNA species (minus strands of bacteriophage Qß RNA) in a series of steps that includes binding the target RNA to a support and separating the desired RNA species bound to the support from other sample components (i.e., cellulose chromatography), and (2) *in vitro*, exponential synthesis of more RNA from the isolated target RNA strands to amplify the amount of desired RNA. The *in vitro* synthesis reaction used Qß replicase to produce about three times the input RNA after four minutes, which was detected as incorporation of radioactive nucleotides and as the generation of

infectious RNA measured in an *in vitro* transfection assay.

174. The purification procedure disclosed by Feix *et al.* is described in more detail by Pollet *et al.*, (1967) who disclosed a multi-step method of purifying bacteriophage Qß minus strands from double-stranded viral RNA (dsRNA) comprising minus and plus strands. In particular, this method includes the steps of contacting a viral RNA sample with a solid support (cellulose) that separates dsRNA from single-stranded RNA (ssRNA), to ultimately produce a purified ssRNA that was predominantly minus strands.

175. The Feix *et al.* reference alone provides all of the method steps recited in claim 1 of the '338 patent because it describes the purification procedure of Pollet *et al.* and a method for amplifying the isolated target polynucleotide *in vitro* to produce more RNA which was detected by both physical and biological methods. Together, the Feix *et al.* and Pollet *et al.* references provide all of the information one skilled in the art would need to make the inventions claimed in the '338 patent obvious.

176. As discussed above, U.S. Patent No. 4,957,858 (Chu et al.) disclosed a method of replicating a reporter nucleic acid using an enzyme called Qß replicase, typically on a processed specimen derived from a raw specimen to remove materials that would otherwise interfere with detection. As disclosed in materials related to the '858 patent, as of March 1985 certain of the inventors of the technology claimed in the patent had conceived of a technique for using Qß replicase for signal amplification that involved capture of the target DNA or RNA upon a solid support such as nitrocellulose or nylon membrane. In an Invention Report and Record dated February 8, 1985, submitted to the Department of Health and Human Services on March 27, 1985, Drs. Lizardi, Kramer and Mills described a technique of nucleic acid hybridization in which a sample containing DNA or RNA "is immobilized on a solid support" and subsequently detected with a recombinant RNA molecule that is "replicated faithfully to generate millions of copies" by using Qß replicase (Disclosure of Invention, pages 1-4). Other materials related to the '858 patent show that as of December 1987, certain of the inventors of the technology claimed in the patent had conceived of a technique for using Qß replicase for signal amplification that involved capture of the target DNA or RNA upon solid supports in accordance with known sandwich hybridization

techniques. *See* Manuscript by, Lizardi *et al.*, "Billion-fold amplification of recombinant-RNA hybridization probes," submitted for publication 12/18/81 (VI 104595-VI 104618), particularly page 12 (VI 104606), first full paragraph and reference cited therein. A related U.S. Patent, U.S. Patent No. 5,989,817 (Soderlund, *et al.*, issued November 23, 1999), filed before the filing date of the '338 patent, discloses assay methods for nucleic acids employing hybridization techniques where, following a capture step, detector probes are incorporated into target nucleic acids and amplified.

177. Vysis never achieved any commercial success with the inventions claimed in the '338 patent. Vysis never developed any product with such methods, never achieved FDA approval of such a product, and never obtained any revenue from such a product.

178. Gen-Probe contends that no evidence concerning Gen-Probe's conduct with respect to, or products incorporating, TMA methods will provide relevant evidence in this case as to secondary considerations of non-obviousness, which must be determined with respect to the claimed invention (e.g., an invention incorporating non-specific amplification).

179. If evidence of Gen-Probe's conduct and products is determined for any reason to be relevant in this case, Gen-Probe will demonstrate that the evidence relied on by Vysis is insufficient to overcome the weight of the prior art as to obviousness and secondary considerations concerning Vysis' own conduct. If evidence of Gen-Probe's conduct and products is determined for any reason to be relevant in this case, Gen-Probe will demonstrate a lack of nexus between its anticipated commercial success and the technology disclosed in the '338 patent. If evidence of Gen-Probe's conduct and products is determined for any reason to be relevant in this case, Gen-Probe will demonstrate that it did not "copy" any Vysis technology. Gen-Probe will further demonstrate that its so-called "collaboration" with Vysis resulted solely from Vysis' offers to explore settlement of certain prior litigation known as *Regents v. Kohne* and *Center for Neurolgic Study v. Kohne*. Gen-Probe will further show that it obtained a license to the '338 patent only after Vysis took the position that the patent was valid and infringed by Gen-Probe's blood screening assay, and that the license was acquired in view of Vysis' demonstrated willingness and capability to commence and maintain meritless litigation, as shown by the *Regents v. Kohne* and *Center for*

Neurolgic Study v. Kohne cases.

180. The invention claimed in the '338 patent was publicly disclosed not later than August 23, 1989, when Vysis' application for European Patent publication no. 0 328 829 A2 was published. The European patent '829 application was a copy of the same application that directly led to issuance of the '338 patent. As a copy of the U.S. application, the European application necessarily disclosed the invention claimed in the '338 patent.

F. THE '338 PATENT IS UNENFORCEABLE

181. Applicants for patents have a general duty of candor and good faith in their dealings with the Patent and Trademark Office (the "Patent Office") and an affirmative obligation to disclose to the Patent Office all information that they know to be material to the examination of a pending application pursuant to 37 C.F.R. § 1.56. This duty extends to the applicants and their representatives, such as their attorneys, and all others associated with the prosecution, including every person who is substantively involved in the preparation or prosecution of the application.

182. The applicants knowingly and willfully concealed and misrepresented material evidence during the prosecution of the '338 patent applications and that by such inequitable conduct, the '338 patent is unenforceable against Gen-Probe for the reasons that follow.

1. Applicants' Failure to Disclose all Material Art Known to Them During the Prosecution of the '338 Patent and Misrepresentations as to the State of the Art.

183. Despite their intentional failure to disclose the fatal defect in their claim of priority in the '080 application, the applicants continued to prosecute the claims of that application.

184. During the course of its prosecution of the claims that ultimately issued in the '338 patent, the applicants concurrently presented counterpart patent applications and patent claims to international and foreign patent offices. During the course of the examination and prosecution of those counterpart applications and patent claims, the European Patent Office, for one, identified and disclosed to the applicants prior art material to the prosecution of the '338 patent claims that was not before or considered by the United States Patent and Trademark Office in the examination of the '338 patent. For example, among this prior art of record in the European Patent Office proceedings but not in the United States Patent Office was the following: EP-A-0200362 (Cetus

Corp.); EP-A-0265244 (Amoco Corp.); EP-A-0154505 (Ortho Diagnostic Systems, Inc.); WO-A-8605815 (Genetics Int'l Inc.); and WO-A-8701730 (Yale Univ.).

185. Moreover, further material information known to the applicants was not disclosed to the Patent Office. For example, in a trip report dated July 22, 1987, inventor Jonathon Lawrie detailed a visit that he made to the Second Annual ASM Conference on Biotechnology during June 25-28, 1987. The trip report discusses a presentation made by T. Gingeras of SIBIA concerning assays combining the procedures of target capture and amplification. The trip report also notes that a similar presentation was made by T. Gingeras the previous year, 1986, which Dr. Lawrie attended. The fact that Dr. Lawrie attended T. Gingeras' presentation concerning assays combining target capture with amplification constitutes information that is material to the patentability of the '338 patent and should have been disclosed to the Patent Office. Nothing in the file history of the '338 patent indicates that T. Gingeras' work was ever disclosed to the Patent Office by the applicants.

186. Additional references known to applicants to be material to the examination of patent applications for the invention of the '338 patent were not disclosed by applicants to the Patent Office. These references included U.S. Patent No. 4,957,858 (Chu *et al.*, September 18, 1990) and Manuscript by Lizardi *et al.*, "Billion-fold amplification of recombinant-RNA hybridization probes," submitted for publication 12/18/81 (VI 104595-VI 104618), particularly page 12 (VI 104606), first full paragraph and reference cited therein. This manuscript was in the possession of inventor Jonathon Lawrie in December, 1987

187. Notwithstanding the applicants' duty to disclose all material information to the Patent Office, the applicants failed to disclose the foregoing prior art to the Patent Office. In addition, upon filing the application which led to the issuance of the '338 patent, the applicants did not submit a Form 1449, citing all known material art to the Patent Office, as required to ensure that all known material art is considered by the Patent Office. The applicants knowingly and intentionally failed to submit a Form 1449 and concurrently failed to apprise the Patent Office of prior art identified in the European Patent Office proceedings and in prior proceedings on related United States patent applications, in order to deceive the Patent Office and prevent it from

considering all relevant prior art. For example, once the '080 application was filed and applicants thereby incurred a duty to disclose additional references post-dating December 21, 1987, applicants were required to inform the Patent Office of the public disclosure on August 23, 1989 of applicants' application for European Patent publication no. 0 328 829 A2 and the publication of articles in the United States by the inventors describing the invention. The European patent '829 application was a copy of the same application that directly led to issuance of the '338 patent. As a copy of the U.S. application, the European application disclosed the invention claimed in the '338 patent and was material.

188. During prosecution of the application that lead to the issuance of the '338 patent, it was the examiner's position that modification of the known technique of amplification (by purifying a target nucleic acid from a mixture of nucleic acids using a solid support) was recognized as offering an advantage that would render this improvement an obvious one. Collins et al. took the opposite position that the "evidentiary record of the prior art did not teach purifying target nucleic acids prior to amplification."

189. During prosecution of the '080 application, the applicants submitted a declaration of David H. Persing, M.D., Ph.D. Paragraph 12 of that declaration states:

> Since the addition of such isolation steps would be costly and time consuming, would further complicate the assay and was generally believed to be unnecessary; those who are adding amplification to their nucleic acid hybridization assays had a strong incentive to avoid the addition of target isolation steps to their hybridization assays. It was not until much later that it became apparent that non-specific amplification was occurring despite the careful selection of primer, i.e., that even careful selection of primers would not permit the selective amplification of a particular nucleic acid. I believe this realization did not occur until after December 1987.

190. Subsequent to the Persing Declaration, the examiner allowed the claims of the application. The examiner's reasons for allowance stated "the art at the time of filing did not recognize that the efficiency of PCR amplification would decrease due to the presence of contaminants in the sample and therefore provided no motivation to purify a target sample from a heterogeneous sample of nucleic acid prior to amplification. Having not recognized the problem,

applicants' solution therefore, while utilizing routine methodology to modify PCR amplification techniques, would not have been obvious at the time that the invention was made. The Declaration of Dr. David Persing, further supports this conclusion...." (Statement of Reasons for Allowance mailed October 16, 1997).

191. It is evident from the above that throughout prosecution, inventors Collins et al., by means of attorney argument and the declaration of Dr. Persing, affirmatively asserted that as of the December 21, 1987 filing date, those skilled in the art would not have considered isolation of target nucleic acids before applying amplification techniques. This affirmative assertion is what persuaded the examiner to allow the claims.

192. The applicants knew that this assertion was not true. As set forth above concerning the issues of obviousness and anticipation based on the prior art available as of December 21, 1987, the combination of target isolation (capture) on a solid support with amplification of the isolated polynucleotide is disclosed in the prior art, and the motivation to combine target capture with amplification is also in the prior art.

193. Moreover, the Chu '858 patent teaches an assay in which a reporter polynucleotide is amplified using the enzyme Qß replicase. The Chu patent teaches that the assay method is carried out on a sample which has been processed "to remove materials that would interfere with detection" (see Chu '858, col. 7, ll. 7-15).

194. As of August 27, 1987, prior to the filing date of the '338 patent, Vysis and/or its predecessor Gene-Trak were well aware that others in the art had developed nucleic acid amplification strategies. One such strategy was a Qß replicase method for which a patent had been applied for. That application matured as the Chu '858 patent. Because the Chu '858 patent disclosed that others were aware of the improved results that could be obtained by separation of the nucleic acid target from the sample before amplification, by withholding the '858 patent from the examiner the applicants affirmatively misled the examiner during prosecution with regard to the state of the art as of the December 21, 1987 filing date of the Collins '338 patent.

195. The applicants were also aware of other material which taught the concept of polynucleotide separation from a sample and the application of Qß replicase amplification. For

example, a report submitted for publication in the name of Paul M. Lizardi et al. was provided to the applicants at least by December 22, 1987, its received date. The article had been submitted for publication on December 18, 1987. That article states, "in practice, the sensitivity of the assays will be determined by the efficiency of the method used to remove non-specifically bound probes. There are a number of promising methods for reducing this background, including 'sandwich hybridization' techniques. By combining an effective background reduction technique with the enormous amplification that is inherent in the use of recombinant probes, it should be possible to develop assays that are able to detect even a small infectious agent in a clinical sample." (Page 12.) By not providing this information to the examiner, the applicants were able to mislead the examiner regarding the true state of the art surrounding the combination of isolation and amplification.

196. The evidence also demonstrates that certain Qß replicase related patent applications, including that which matured into the Chu '858 patent, were of such potential commercial significance that Vysis' predecessor, Gene-Trak systems, obtained a license to operate within the confines of the Chu '858 patent.

197. The applicants were obligated to disclose the Chu '858 patent to the attention of the examiner during prosecution of the Collins '338 patent for several reasons:

(a) First, the original claims of the Collins '338 patent did not differentiate between amplification of the probe and amplification of the target. Original Claim 1 merely required contacting the sample potentially containing the target with a first support capable of specifically associating with the target under binding conditions, separating the support from the remaining sample to form a "removal product" and subjecting the "removal product" to amplification. The claim does not specifically state that the target is amplified; indeed, the definition of "amplify" set forth at column 2 of the patent broadly encompasses amplification of any molecule whose presence indicates the presence of the target. Accordingly, the Chu '858 patent anticipated the original claims of the Collins application. Hence, the Chu '858 patent would have been highly material prior art;

(b) Second, the Chu '858 patent has a typographical error with regard to the

filing date of the application which matured into the '858 patent. The face of the patent indicates the filing date is April 16, 1988. This is a typographical error; the filing date is actually April 16, 1986 (as subsequently established by a Certificate of Correction). The correct filing date was known to the applicants in that it was referred to in licensing documents. Because the Chu patent contains an error with regard to the filing date, the examiner would not have considered and cited the Chu patent as being representative of the prior art because on its face its filing date was subsequent to the filing date of the Collins '338 patent. Hence, the examiner would have considered the Chu '858 patent unavailable. The Chu '858 patent should have been brought to the examiner's attention under these circumstances.

(c) Third, because those prosecuting the Collins application had advised the examiner that those skilled in the art at the time the invention was made would not have isolated the probe/target complex prior to amplification, they were obligated to advise the examiner regarding the Chu '858 patent and its applicability to the claims of the Collins application because it refutes an assertion made during prosecution. See 37 C.F.R. §1.56(b)(2)(ii).

2. Applicants' Misrepresentations About The Scope of the '080 Application

198. During prosecution of the application that lead to the issuance of the '338 patent, it was the examiner's position that modification of a known technique of amplification (by purifying a target nucleic acid from a mixture of nucleic acids using a solid support) was recognized as offering an advantage that would render this improvement an obvious one. Collins et al. took the opposite position that the "evidentiary record of the prior art did not teach purifying target nucleic acids prior to amplification."

199. During prosecution of the '080 application, the applicants submitted a preliminary amendment on December 5, 1995. This amendment was submitted almost eight years after applicants filed the first application claiming similar subject matter. In the December 5, 1995 amendment, applicants for the first time suggested that the subject matter represented an improvement to PCR amplification methods, although applicant's knew that the '080 application did not encompass specific amplification methods such as PCR and knew that they had not once

suggested otherwise during the eight years in which they had prosecuted various related applications.

200. During prosecution of the '080 application, the applicants submitted a declaration of David H. Persing, M.D., Ph.D. on July 9, 1997. The Persing declaration was entirely focused on PCR amplification. The Persing declaration sought to overcome an obviousness rejection by contending that those skilled in the art did not recognize until after December 1987 that non-specific amplification occurred during PCR amplification despite the careful selection of primers.

201. By this course of conduct, applicants sought to misrepresent the nature of their invention and claim that invention as an improvement to PCR. Applicants knew these representations were false and made them with the intent to deceive the Patent Office. Applicants' course of conduct, including the Persing declaration, successfully misled the Examiner into believing that the '338 patent encompassed specific amplification. In the Examiner's October 13, 1997 statement of reasons for allowance of the patent, the Examiner stated: "The claims are drawn to methods of PCR amplification..."

3. Applicants' Misrepresentations About Mullis, U.S. Patent No. 4,683,202

202. During the course of that continued prosecution of the '080 application, the Patent Office rejected applicants' proposed claims to a method of nucleic acid amplification on the grounds of the disclosure of prior art that included the Mullis patent (U.S. Patent 4,683,202). In response, the applicants argued that the prior art did not teach or disclose purification of a target nucleic acid prior to amplification, yet, that argument was false. Specifically, in their December 5, 1995 Preliminary Amendment, the applicants made the following statements regarding the Mullis patent:

> Applicants submit the Examiner's conclusion is the product of an improper picking and choosing of selective disclosure from the cited references to obtain Applicants' invention and that when the references are considered for all that they teach the references do not disclose or suggest Applicants' invention. For example, while it is true that Mullis (U.S. No. 4,683,202) discloses DNA amplification and some improved sensitivity and ability to isolate specific nucleoside sequences, Mullis also teaches away from Applicants' invention. Specifically, Mullis teaches:

> The present invention obviates the need for extensive purification of the product from a complicated biological mixture.

(Col. 2, lines 32-34). Mullis reaffirmed this teaching later in the disclosure:

> ***It is not necessary that the sequence to be amplified be present initially in a pure form; it may be a minor fraction of a complex mixture ... or a portion of a nucleic acid sequence due to a particular microorganism which organism might constitute only a very minor fraction of a particular biological sample.***

(***Col. 5, lines 49-56***). Plainly, Mullis teaches that the amplification method of his invention does not include purification before amplification and, in fact, does not require purification. Thus, Mullis teaches away from Applicants' invention.

12/5/95 Preliminary Amendment at p. 16 [emphasis added]. The applicants repeated this representation to the Patent Office regarding the teachings of Mullis in the Amendment filed on October 18, 1996, at pp. 11-12.

203. The paragraph cited by the applicants from the Mullis patent reads in whole:

> Any source of nucleic acid, in ***purified*** or nonpurified form, can be utilized as the starting nucleic acid or acids, provided it contains or is suspected of containing the specific nucleic acid sequence desired. Thus, the process may employ, for example, DNA or RNA, including ***messenger RNA***, which DNA or RNA may be single stranded or double stranded. In addition, a DNA-RNA hybrid which contains one strand of each may be utilized. A mixture of any of these nucleic acids may also be employed, or ***the nucleic acid produced from a previous amplification reaction*** herein using the same or different primers may be so utilized. The specific nucleic acid sequence to be amplified may be only a fraction of a larger molecule or ***can be present initially as a discrete molecule, so that the specific sequence constitutes the entire nucleic acid***. It is not necessary that the sequence to be amplified be present initially in a pure form; it may be a minor fraction of a complex mixture, such as a portion of the .beta.-globin gene contained in whole human DNA or a portion of nucleic acid sequence due to a particular microorganism which organism might constitute only a very minor fraction of a particular biological sample. The starting nucleic acid may contain

> more than one desired specific nucleic acid sequence which may be the same or different. Therefore, the present process is useful not only for producing large amounts of one specific nucleic acid sequence, but also for amplifying simultaneously more than one different specific nucleic acid sequence located on the same or different nucleic acid molecules.

(Col. 5, lines 34-63), emphasis added, underlined is the portion selectively cited by the applicants). Thus, contrary to the applicants' representation to the Patent Office, the omitted portion of the paragraph cited by the applicants expressly teaches that purification combined with the amplification invention was disclosed in the art, thereby validating the Examiner's rejection.

204. In addition to the excluded portion of the paragraph of the Mullis patent, the very next paragraph in the Mullis patent states:

> The nucleic acid or acids may be obtained from any source, for example, from plasmids such as pBR322, from cloned DNA or RNA, or from natural DNA or RNA from any source, including bacteria, yeast, viruses, and higher organisms such as plants or animals. ***DNA or RNA may be extracted from blood, tissue material such as chorionic villi or amniotic cells by a variety of techniques such as that described by Maniatis et al., Molecular Cloning A Laboratory Manual (New York: Cold Spring Harbor Laboratory, 1982), pp. 280-281.***

(Col. 5, line 64-col. 6, line 6 [emphasis added]). Maniatis, et al., is a methods manual that teaches a variety of techniques for purifying RNA or DNA from blood, tissue or other cellular material. At pages 197-198 of Maniatis, et al., this reference teaches the purification of mRNA on a solid support using a probe. Thus, the very next paragraph of the Mullis patent following the selective citation by the applicants incorporates a disclosure of ***how*** to purify a nucleic acid from a sample prior to amplification. The applicants' selective removal of the first half of the cited paragraph that fully supported the Examiner's rejection based on Mullis and the following paragraph's implicit teaching of how to purify a nucleic acid from a sample prior to amplification evidence the knowing and intentional nature of the applicants' misrepresentation of the Mullis reference.

4. Applicant's Misrepresentations In Connection With The Request for Certificate of Correction Filed for the '338 Patent

205. By the December 14, 1998, Request for Certificate of Correction, the applicants

intentionally misrepresented to the Patent Office that the prior intentional choices made by patent counsel as to which "correction" was sought were "mistakes" and that those mistakes were of "minor character." The applicants knew that the true facts were that intentional choices by patent counsel were not "mistakes" under applicable law and that defects which rendered the '338 patent invalid could not constitute mistakes "of minor character."

206. By the December 14, 1998, Request for Certificate of Correction the applicants attempted to cure fatal defects in the '338 patent by, among other things, intentionally misrepresenting to the Patent Office that the prior intentional choices made by patent counsel as to which "correction" was sought resulted from errors made in good faith by the applicants. The applicants knew that the true facts were neither the request for certificate of correction nor any act after the abandonment of the '505 application was undertaken by applicants in good faith.

207. By the December 14, 1998, Request for Certificate of Correction, the applicants attempted to cure fatal defects in the '338 patent by, among other things, intentionally misrepresenting to the Patent Office when applicants had discovered the mistakes as to which correction was sought. The applicants knew that the true facts were that defects had been discovered earlier than they disclosed to the Patent Office. Applicants and their counsel represented that the so-called "Error 2" only recently been identified, when in fact they knew that "Error 2" had been identified in 1995 and an amendment requested on March 8, 1995 in the course of the prosecution of application 08/400,657.

208. By the December 14, 1998, Request for Certificate of Correction, the applicants attempted to cure fatal defects in the '338 patent by, among other things, intentionally misrepresenting to the Patent Office that the '505 application had been inadvertently and unintentionally abandoned. The applicants made this representation knowing that the true facts were that the '505 application was intentionally abandoned.

209. The applicants further represented in the Request for Certificate of Correction for the '338 patent that the '338 patent was a continuation of the '826 application. However, the '338 patent could not be a continuation of the '826 application, because the disclosure of the '338 patent was not identical to the disclosure of the '826 application.

210. The applicants knew that the '338 patent could not be a continuation of the '826 application, and that through the aforementioned Certificate of Correction, the applicants knowingly and intentionally misrepresented their knowledge with the intent of deceiving the U.S. Patent and Trademark Office.

211. The misrepresentations of applicants set forth herein were material. As a direct result of the conduct of applicants set forth herein, the certificate of correction was entered by the Patent Office on September 7, 1999.

5. Applicants' Misrepresentation in their Petition under 37 C.F.R. §1.182

212. The applicants misrepresented legal authority to the Patent Office in their December 14, 1998 petition under 37 C.F.R. § 1.182, in that that they knew that the legal authority presented to the Patent Office to support the petition to amend the '826 application and cure the otherwise fatal priority defect in the '338 patent did not stand for the proffered proposition and that the applicants knowingly misrepresented this legal authority to the Patent Office with the intent to deceive the Patent Office.

213. In petitioning to amend the three abandoned applications, applicants did not disclose to the PTO that they were seeking to circumvent applicants' abandonment of the '505 application nor did they even disclose the existence of that prior application.

214. In petitioning in December 1998 to amend the three abandoned applications, applicants did not disclose to the PTO that they had discovered the defect they sought to amend no later than March 8, 1995 and that an amendment had been requested to the '657 application on that date.

215. As direct result of the conduct of applicants set forth herein, the petitions to amend the abandoned applications were granted by the PTO in a decision mailed July 1, 1999.

6. Applicants' Failure to Disclose The Known Inoperativeness of their Exponential Non-specific Amplification Techniques

216. In their specification, applicants' purported to describe two exponential non-specification amplification techniques. Example 6, for example, purports to describe a scheme for exponential non-specific amplification using random hexamer primers whereas Example 7

purports to describe the use of Qß replicase to exponentially amplify target nucleic acids. Both examples are written in "prophetic" form suggesting that Vysis had not actually attempted to reduce either of those examples to practice.

217. As to Example 6, any suggestion that Vysis had not sought to reduce that invention to practice prior to the filing date of the '920 application is false. In reality, a team of Gene Trak scientists including Dr. Scott Decker struggled for months prior to the December 21, 1987 filing date of the '920 application to attempt to practice the technique disclosed in Example 6 before ultimately concluding that Example 6 would not result in amplification of a target polynucleotide. Gene Trak never achieved amplification using the technique disclosed in Example 6.

218. As to Example 7, neither Gene Trak nor Vysis ever attempted to implement this Example. Gen-Probe believes that at the time of filing of the '920 application, Vysis had no reasonable expectation that Example 7 was then operative or would ever become operative due to the highly specific nature of the Qß replicase enzyme.

219. The applicants for the '338 patent had a duty to disclose the foregoing material facts of inoperativeness to the Examiner. Particularly where those facts were know prior to filing, the applicants had a duty to disclose that they had already attempted and failed to practice their prophetic examples.

G. THE '338 PATENT IS UNENFORCEABLE ON THE GROUND OF LACHES

220. The foregoing discussion of the prosecution history of the '338 patent demonstrates that the applicants intentionally, unreasonably, and inexcusably delayed in the prosecution of the invention claimed in the '338 patent.

221. Vysis unreasonably and without explanation delayed the prosecution of the applications for the inventions claimed in the '338 patent from the filling of the 136,920 application on December 21, 1987 through at least the issuance of the patent on May 12, 1998, a period of 10½ years.

222. Vysis delayed the prosecution of applications for the inventions claimed in the'338 patent unreasonably and without explanation by (among other things) obtaining extensions of time to respond to office actions by the Patent Office, failing to respond on the merits to such office

actions by the Patent Office and instead abandoning patent applications while under rejection and filing continuation applications. Vysis repeated this practice many times over the 10½-year period in which the claims of the '338 patent were prosecuted.

223. Additionally, Vysis delayed the prosecution of its claims by improper and untimely claims of priority, including but not limited to contending that the '080 application was a divisional of '757 application, the improper claim that the '080 application was a continuation of the '826 application, and the delay in contending that the '080 application was a continuation of the '826 application.

224. Gen-Probe denies that the '338 patent encompasses any of Gen-Probe's products. Alternatively, however, if the '338 patent covers Gen-Probe products, Gen-Probe contends that it was injured by Vysis' unreasonable and unexplained delay in prosecuting applications for the inventions claimed in the '338 patent. These injuries include Vysis obtaining extended patent protection for the inventions claimed in the '338 patent by delaying issuance of the patent. Additionally, during the period of time that the prosecution was delayed, Gen-Probe made numerous product design and product development decisions with respect to technologies related to, but neither the same as or equivalent to, those claimed in the '338 patent.

H. VYSIS ABANDONED THE INVENTIONS CLAIMED IN THE '338 PATENT.

225. As set forth above, on February 5, 1993, the applicants intentionally abandoned U.S. patent application 07/944,505 with full knowledge of their rights. Applicants thereafter, intentionally and with full knowledge of their rights, took no further action with respect to prosecuting claims for the inventions that had been the subject of the '505 application until May 3, 1994. Applicants elected this course of action (and inaction) in response to rejections by the Patent Office of the '920, '967, and '505 applications, of which certain of the office actions were first action final rejections. Applicants took this action, in part, in response to fiscal constraints imposed at the time on Vysis. Applicants' abandonment of the '505 application and subsequent inaction establish that applicants abandoned the inventions claimed therein in the United States.

I. VYSIS HAS COMMITTED ACTS OF UNFAIR COMPETITION

226. Based on the facts relating to the scope, invalidity and unenforceability of the '338

patent, as described above, Vysis knew or should reasonably have known that these facts establish that the claims of the '338 patent are invalid and/or unenforceable and do not cover Gen-Probe's TMA blood screening assay. In the first half of 1999, Vysis repeatedly asserted, orally and in writing, that Gen-Probe's TMA blood screening assay was encompassed by the claims of the '338 patent. By asserting that the claims of the '338 patent were valid and covered Gen-Probe's NAT products and by requiring Gen-Probe to take a license thereto in order to avoid litigation, Vysis acted, and continues to act, unfairly, inequitably and in bad faith.

227. Vysis' actions constitute unlawful, unfair or fraudulent business practices under California Business & Professions Code Sections 17200, *et seq.*

III. CONTENTIONS OF LAW

A. GEN-PROBE'S PRODUCTS DO NOT INFRINGE THE '338 PATENT

228. It is unlawful to make, use, offer to sell, or sell any patented technology, within the United States, or import into the United States any patented invention during the term of the patent without authorization from the patent owner. 35 U.S.C. § 271. Gen-Probe is licensed by Vysis under the '338 patent, and hence, cannot technically infringe the claims of the '338 patent. Nevertheless, Gen-Probe brought this action believing that, notwithstanding the license granted to it by Vysis, Gen-Probe is entitled to a judgment that its blood screening products do not infringe any valid claim of the '338 patent.

229. By virtue of its Order dated June 20, 2001, the Court has already entered judgment in favor of Gen-Probe adjudging that Gen-Probe does not literally infringe the claims of the '338 patent on the basis of the Court's construction of the term "amplifying" the target polynucleotide to include only methods of non-specific amplification. Thus, the only remaining issue relating to non-infringement is whether Gen-Probe's blood screening products infringe the claims of the '338 patent under the Doctrine of Equivalents.

230. As the patent owner, Vysis bears the burden of proof with respect to infringement. Vysis must establish by a preponderance of the evidence that Gen-Probe's products infringe a valid claim of the '338 patent under the Doctrine of Equivalents.

231. Vysis asserts that, absent the existence of the parties' license, Gen-Probe would

infringe claims 1, 2, 3, 4, 5, 7, 8, 9, 10, 11, 13, 14, 24 and 25 of the '338 patent. Gen-Probe denies these allegations.

232. Claims 1, 2, 3, 4, 5, 7, 8, 9, 10, 11, 13 and 14 are method claims that are technically infringed in the first instance, if at all, by Gen-Probe's customers that actually perform the diagnostic methods enabled by Gen-Probe's kits.

233. Gen-Probe's infringement exposure for technical infringement of the forgoing method claims is thus focused on its alleged liability for inducing "technical" infringement by Gen-Probe's customers who use the Gen-Probe NAT kits in accordance with the instructions and protocols Gen-Probe provides with those diagnostic kits.

234. Claims 24 and 25 of the '338 patent are kit claims that are written in "means-plus-function" format. In order for Vysis to prove literal infringement of those means-plus-function claims, Vysis would have had to show that the elements of Gen-Probe's kits perform the identical function to the function recited in the claims. The Court has previously held that these claims are not literally infringed because specific amplification techniques like TMA and PCR do not perform the identical function of the amplification means disclosed in the '338 patent. However, even if Vysis could have established that Gen-Probe's products perform the identical function of the "amplification means"– which it cannot, it would also have to show that Gen-Probe's kit elements use the same structure or materials described in the specification, or their equivalents.

235. Because the individual elements and techniques employed in Gen-Probe's products were generally known and used prior to the filing date of the '920 application (and certainly prior to the '080 application), Vysis is not entitled to seek a still further equivalents analysis as to Claims 24 and 25. *See Chiuminatta Concrete Concepts, Inc. v. Cardinal Indus., Inc.*, 145 F.3d 1303, 1311 (Fed. Cir. 1998). In other words, because the general technology and components used in Gen-Probe's accused products consisted of elements known or anticipated in December 1987 (and certainly by May 1994 – the date of filing for the '080 application), Vysis is not entitled to an "equivalent of a equivalent" inquiry. *See id.* ("[G]iven the prior knowledge of the technology asserted to be equivalent, it could readily have been disclosed in the patent. There is no policy based reason why a patentee should get two bites of the apple.").

236. As to claims 1, 2, 3, 4, 5, 7, 8, 9, 10, 11, 13 and 14, in order to establish infringement under the doctrine of equivalents the patent owner must prove that the differences between the claim element at issue and the corresponding element in the accused product are "*insubstantial.*" *Warner-Jenkinson v. Hilton-Davis Chemical Co.*, 520 U.S. 17, 28-30 (1997); *Gamma-Metrics Inc. v. Scantech Ltd.*, 52 USPQ2d 1568, 1574 (S.D. Cal. 1998) (Huff, J.). The issue is frequently determined by asking whether the accused product "performs the same function, in the same way, to achieve the same result" as the claim element at issue. *Warner-Jenkinson*, 520 U.S. at 39; *Gamma-Metrics Inc.*, 52 USPQ2d at 1574. Under the "all elements" rule, each element contained in a patent claim is deemed material to defining the scope of the patented invention, and thus each individual element of the claim must be considered, *not the invention as a whole. Warner-Jenkinson Co.*, 520 U.S. at 29-30; *Loral Fairchild Corp. v. Sony Corp.*, 181 F.3d 1313, 1322 1327 (Fed. Cir. 1999); *Gamma-Metrics Inc.* 52 USPQ2d at 1574. Thus the "function-way-result" comparison of the accused product to the patent claim must be made on an element-by-element basis. *Stryker Corp. v. Davol Inc.*, 10 F.Supp.2d 841, 845 (W.D. Mich. 1998).

237. As set forth in the factual discussion in Section II, above, the facts show that *substantial* differences exist between generic forms of specific amplification and non-specific amplification, when considered as separate elements and when considered in the "context of the claims" under the "all elements rule." TMA does not perform substantially the same function in substantially the same way to achieve substantially the same result as the non-specific methods of amplification literally encompassed by the claims of the '338 patent.

238. Specific amplification does *not* perform the same function, in the same way, to achieve the same result as non-specific amplification. The inventors and other employees of Gene-Trak/Vysis admitted that these methods were "different" and further admitted that non-specific amplification was the "opposite" of specific amplification. The text of the '338 patent specification itself admits and highlights the differences between the two methods of amplification:

> Amplification of the target nucleic acid sequences, because it follows purification of the target sequences, can employ non-specific enzymes or primers (i.e., enzymes or primers which are capable of causing the replication of virtually any nucleic acid sequence).

> Although any background, non-target, nucleic acids are replicated along with target, this is not a problem because most of the background nucleic acids have been removed in the course of the capture process. *Thus, no specially tailored primers are needed for each test, and the same standard amplification reagents can be used, regardless of the targets.*

['338 Patent, at 30:38-40 (emphasis added).] This statement provides an admission of the substantial differences between non-specific and specific amplification:

- that non-specific amplification utilizes non-specific enzymes or primers "(*i.e.*, enzymes or primers which are capable of causing the replication of virtually any nucleic acid sequence)."
- that with non-specific amplification the "same standard amplification reagents can be used, regardless of the targets."
- that non-specific amplification results in "background, non-target, nucleic acids [being] replicated along with target."

Id. By differentiating between non-specific and specific amplification in that manner, thus teaching away from the use of specific primers and enzymes, the '338 patent forecloses any possibility that Gen-Probe's TMA method could be considered equivalent to the claimed non-specific amplification techniques. *See Spectra Corp. v. Lutz*, 839 F.2d 1579, 1582 (Fed. Cir. 1988) (clear and uncontroverted statements in patent specification precluded contrary argument of equivalence); *Brenner v. United States*, 773 F.2d 306, 308 (Fed. Cir. 1985).

239. Not only is the *general* technique of TMA significantly different from the claimed non-specific amplification techniques of the '338 patent but the particular embodiment of TMA the Gen-Probe has deployed in its accused products represents an even more distinguishable basis for rejecting a claim of infringement under the Doctrine of Equivalents. Vysis has not attempted to analyze Gen-Probe's specific embodiments and therefore cannot meet its burden of proof on this issue.

240. Finally, the fact that Gen-Probe's products are encompassed by independent patents issued by the United States Patent Office over the express reference to the '338 patent provides additional evidence to substantiate the lack of equivalence between Gen-Probe's products and the claims of the '338 patent. Although this fact of independent patentability is not conclusive, it provides persuasive proof of the substantial differences between Gen-Probe's products.

1. Other Issues

241. The Court's summary judgment order on literal infringement greatly reduces the number of claim construction issues remaining to be resolved. Several issues remain for purposes of invalidity and infringement analysis, however, such as claim scope in connection with evaluating whether certain prior art anticipates the claims of the '338 patent. The remaining claim interpretation issues may be resolved by the Court prior to or during the course of trial in accordance with *Markman v. Westview Instruments, Inc.* 52 F.3d 967 (Fed. Cir. 1995), *aff'd*, 517 U.S. 370 (1996). The issues are identified and discussed below.

242. *"Amplifying the Target Polynucleotide."* Each of the claims asserted by Vysis to be infringed by Gen-Probe's products contains the term "amplifying". As noted above, the Court has already construed the meaning of the term "amplifying" to mean making copies of a target polynucleotide by using methods of non-specific amplification. (June 20, 2001 Order). Additional issues of claim interpretation remain.

(a) For example, Gen-Probe contends that "amplifying the target polynucleotide" includes indirect methods of target amplification, such as by creating an amplification product such as reporter molecules, *i.e.*, "target-like molecules which are capable of functioning in a manner like the target molecule, or a molecule subject to detection steps in place of the target molecule, which molecules are created by virtue of the of the presence of the target molecule in the sample." ('338 patent at col. 2, ll. 9 – 15.)

(b) Gen-Probe further contends that "amplifying the target polynucleotide" includes both *in vitro* and *in vivo* amplification methods. Amplification methods do not need to be useful in a commercial diagnostic kit in order to be included within the scope of the '338 patent claims.

(c) Gen-Probe further contends that "amplifying" does not include mere synthesis of a nucleotide sequence complementary to a sequence in the target.

(d) *"A First Support."* Claims 1, 2, 3, 4, 5, 7, 8, 9, 10, 11, 13, and 14 are asserted by Vysis as being infringed by Gen-Probe. Each of these claims requires the use of a first support that binds to the target polynucleotide. Gen-Probe contends that the term "support" as

used in these claims includes all types of solid phases, including conventional supports such as filters, membranes, and absorbents used in column chromatography or batch separations. For example, the term "support" as used in these claims includes nitrocellulose, oligo(dT) cellulose, hydroxyapatite, streptavidin agarose, and magnetic beads with covalently attached capture oligonucleotides. The term "support" includes solid phases that bind non-specifically as well as specifically with the target polynucleotide. Supports do not need to be useful in a commercial diagnostic kit in order to be included within the scope of the '338 patent.

243. "*A First Support Which Binds to the Target Polynucleotide.*" Claims 1, 2, 3, 4, 5, 7, 8, 9, 10, 11, 13, and 14 are asserted by Vysis as being infringed by Gen-Probe. Each of these claims requires the use of "a first support which binds to the target polynucleotide." Certain of these claims require the first support to include "a probe which binds with the target polynucleotide." To the extent that the term "binds" is construed to mean "a direct attachment" between the first support or probe and the target nucleic acid, then Gen-Probe's products do not employ such a step. (This definition of "a direct attachment" is consistent with the definition of "bind" set forth in The American Heritage Dictionary of the English Language as " to cause to cohere or stick together in a mass.") Gen-Probe's products employ a procedure whereby a capture probe first binds to the target nucleic acid to form a capture probe-target complex. The capture probe then binds to an intermediary probe that is attached to a solid support. Neither the support nor the support-bound probe bind directly to the target.

244. Because the Gen-Probe products do not employ a direct binding procedure whereby the capture probe directly binds to a solid support, the Gen-Probe products also do not literally infringe the '338 patent for this further reason. In addition, the Gen-Probe products do not infringe these claims under the doctrine of equivalents for the reasons set forth in greater detail in the specification of Gen-Probe's patent, United States Patent No. 6,110,678 (the '678 patent"). The absence in Gen-Probe's products of the required direct binding step results in significant and functional differences from the techniques disclosed in the '338 patent.

245. "*Means for Amplifying the Target Polynucleotide.*" As noted above, Vysis asserts that claims 24 and 25 are infringed by Gen-Probe's products. Claims 24 and 25 are directed to a

"kit" for amplifying a target polynucleotide, and these claims use the term "means for amplifying the target polynucleotide." Claim elements drafted in language that merely claims a means for performing a specified function without further reciting the structure, material or acts in support of that means are classified as means-plus-function limitations, which are subject to 35 U.S.C. § 112, paragraph 6. In order to literally meet a means-plus-function limitation, "an accused device must (1) perform the identical function recited in the means limitation and (2) perform that function using the structure disclosed in the specification or an equivalent structure." *Carroll Touch, Inc. v. Electro Mechanical Systems, Inc.*, 15 F.3d 1573, 1578 (Fed. Cir. 1993); *see also Cybor Corp. v. FAS Technologies, Inc.*, 138 F.3d 1448, 1457 (Fed. Cir. 1998) ("Under § 112, ¶ 6, an accused device with structure not identical to the structure described in the patent will literally infringe the patent if the device performs the identical function required by the claim with a structure equivalent to that described in the patent.")

246. The only "structures" disclosed in the specification of the '338 patent to perform the function of "amplification" are the non-specific amplification techniques disclosed in Examples 4, 5, 6 and 7. Based upon the Court's June 20, 2001 Order construing the term "amplification," claims 24 and 25 can be literally infringed only by a structure that performs the identical function as that provided by the non-specific amplification enzymes and primers disclosed in the '338 patent and that represents the same or equivalent structure as those non-specific enzymes and primers. *Carroll Touch*, 15 F.3d at 1578. Inasmuch as the inventors' stated purpose in using non-specific primers and enzymes was to find an amplification technique that was different and presumably non-interchangeable with PCR as well as to simplify and reduce the cost of design and manufacture of amplification reagents so as to allow for the use of amplification reagents that would perform the function of amplifying any nucleic acids present in a sample medium, Gen-Probe's TMA method, in general and as specifically deployed in its accused products, does not perform this identical function. Rather, Gen-Probe's products are specifically designed to perform a significantly different function, that being the amplification of only the desired target nucleic acid.

247. *The Order of the Capture, Amplification, and Detection Steps.* Each of the claims

recites steps that include capture on a solid support and non-specific amplification. The claims do not require that the steps be performed in any particular order to be included within the scope of the patent. Unless the steps of a method actually recite an order, the steps are not ordinarily construed to require one. *Interactive Gift Express Inc. v. Compuserve Inc.*, 256 F.3d 1323, 1342 (Fed. Cir. 2001). Three of the four preferred embodiments sets forth in the '338 patent use a capture step both before and after amplification. Thus, prior art is relevant to the issues of obviousness and anticipation as to the '338 patent if such art discloses amplification and capture on a solid support, regardless of the order in which those steps are performed.

B. THE '338 PATENT IS INVALID

1. Lack of Enablement

a. Enablement requires that the specification teach those skilled in the art how to make and use the *full scope* of the claimed invention without "undue experimentation."

248. Paragraph 1 of Section 112 of the Patent Act requires that the specification of each patent "shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains . . . to make and use the same . . . ." 35 U.S.C. § 112, ¶ 1. The patent's teachings must be commensurate in scope with the breadth of the claim: "[T]o be enabling, the specification of a patent must teach those skilled in the art how to make and use the *full scope* of the claimed invention without 'undue experimentation.'" *Genentech, Inc. v. Novo Nordisk, A/S*, 108 F.3d 1361, 1365 (Fed. Cir. 1997) (citations omitted; emphasis added). Indeed, "[t]he scope of the claims must be less than or equal to the scope of the enablement." *Nat'l Recovery, Inc. v. Magnetic Separation Sys., Inc.*, 166 F.3d 1190, 1196 (Fed. Cir. 1999).

249. The scope of enablement, in turn, "is that which is disclosed in the specification plus the scope of what would be known to one of ordinary skill in the art without undue experimentation." S*ee also In re Goodman*, 11 F.3d 1046, 1050 (Fed. Cir. 1993) ("the specification must teach those of skill in the art 'how to make and how to use the invention as broadly as it is claimed'"). One purpose of the enablement requirement is fairness – a patentee is not allowed to claim more than what is taught by the patent. *Nat'l Recovery*, 166 F.3d at 1195-96.

There must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed. *Enzo Biochem, Inc., v. Calgene, Inc.*, 188 F.3d 1362, 1374 (Fed. Cir. 1999); *In re Vaeck*, 947 F.2d 488, 496 & n.23 (Fed. Cir. 1991).

250. Whether claims are sufficiently enabled by a disclosure in a specification is determined as of the date that the patent application was first filed. *Enzo Biochem, Inc.*, 188 F.3d at 1374.

251. A patent specification is not enabling when it does no more than suggest a "plan" or state an "invitation" for those of skill in the art to experiment using suggested methods, but does not provide sufficient guidance or specificity as to how to execute that plan. *Genentech, supra,* 108 F.3d at 1366.

252. A number of factors may be considered in determining whether a disclosure would require "undue experimentation." These factors are as follows:

> the quantity of experimentation necessary;
> the amount of direction or guidance presented;
> the presence or absence of working examples;
> the nature of the invention;
> the state of the prior art;
> the relative skill of those in the art;
> the predictability or unpredictability of the art; and
> the breadth of the claims.

Enzo Biochem, Inc., supra, 188 F.3d at 1374. Not all of the factors need to be reviewed when determining whether a disclosure is enabling. *Id.*

253. The required scope of enablement of the specification varies inversely with the degree of unpredictability in the art. *In re Angstadt*, 537 F.2d 498, 502 (C.C.P.A. 1976). For claimed inventions in the biological arts, the required level of disclosure is much greater than, for example, the disclosure that would be required of an invention involving a "predictable" factor such as a mechanical or electrical element. *Enzo Biochem, Inc., supra*, 188 F.3d at 1374; *In re Vaeck, supra,* 947 F.2d at 496; 3 Donald S. Chisum, Chisum on Patents, § 7.03[4][d][i], at 7-58 (1999). The invention claimed in the '338 patent of methods of target capture and amplification of nucleic acids clearly falls within the unpredictable biological arts. As such, if a patentee's claims

are sufficiently broad to encompass all possible permutations of an element, then the disclosure of one embodiment will not be sufficient. *Id., see also In re Goodman*, 11 F.3d 1046, 1050 (Fed. Cir. 1993); *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 927 F.3d 1200, 1213-14 (Fed. Cir.), *cert. denied*, 502 U.S. 856 (1991).

b. The '338 patent claims necessarily encompass all manner of non-specific amplification, particularly including exponential amplification as set forth in Examples 6 and 7, and must encompass any type and sequence of nucleic acid.

254. As construed by this Court, the claim term "amplifying" of the '338 patent covers non-specific amplification:

> Based on the explicit language of the specification, the repeated references to non-specific amplification methods, and the absence of any reference to specific amplification or PCR, the Court construes the term "amplifying" as found in the claims of the '338 patent to encompass only non-specific amplification. The Court finds that one of ordinary skill in the art as of December 1987 would have understood from the specification that the inventors' method combined target capture and non-specific amplification.

[June 20, 2001 Order at 10.] For the same reasons that compel the conclusion that the term "amplifying" is limited to non-specific amplification, that term also includes all manner of practice of that generic technique.

255. As noted in Section II, above, Examples 6 and 7 represent at least two of the inventors' preferred embodiments of non-specific amplification claimed in the patent. Because they represent preferred embodiments, the non-specific amplification techniques they purport to disclose are presumed to be encompassed within the scope of the amplification term of the claims. *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996).

256. In *Vitronics*, the Federal Circuit held that patent claims must be construed consistently with the specification and the preferred embodiments described therein. *Vitronics*, *supra*, 90 F.3d 1576, 1583. Indeed, the Federal Circuit has held that a claim interpretation in which a preferred embodiment would *not* fall within the scope of a patent claim "is rarely, if ever, correct and would require highly persuasive evidentiary support . . . " *Id.; accord, Moline Mfg. Co. v. United States Int'l Trade Comm'n*, 75 F.3d 1545, 1550 (Fed. Cir. 1996). As the Court in

Moline stated, "it is unlikely that an inventor would define the invention in a way that excluded the preferred embodiment, or that persons of skill in this field would read the specification in such a way." *Id.* at 1550.

257. Similarly, the doctrine of claim differentiation provides independent confirmation that the inventors meant to include all of the examples of non-specific amplification within the scope of the "amplification term." Briefly stated, the doctrine of claim differentiation provides that the construction of the language in one claim of a patent must be undertaken with appropriate consideration to the language in the other claims of the patent. See *e.g., Chisum on Patents*, § 18.03[6]. One corollary of the doctrine helps confirm that an otherwise unrestricted independent claim necessarily encompasses greater breadth than a restricted dependent claim.

258. With respect to the '338 patent, dependent claim 5 claims the use of Qß replicase as the claimed amplification polymerase. However, the only embodiment that describes the use of the Qß replicase enzyme as an amplification polymerase is Example 7. As such, the inventors must have intended to encompass Example 7, among others, within the scope of dependent claim 5. In turn, based upon the doctrine of claim differentiation, one of ordinary skill would also conclude that claim 4, from which claim 5 depends, and claim 1, from which claim 4 depends, encompass at least Example 7 and, in the absence of any other limitation, would also encompass all the other preferred embodiments, including Example 6.

259. Thus, because the claims encompass *at least* Examples 6 and 7, and indeed are broader than these embodiments, the Court should construe the "amplification" term of the claims of the '338 patent to encompass the full extent of the described and illustrated non-specific amplification techniques. In conjunction with the Court's June 20th construction, Gen-Probe submits that the Court should construe that term as follows:

> the term "amplifying" as found in the claims of the '338 patent encompass only non-specific amplification. Within the general category of non-specific amplification, the term further includes all manner of implementation of that technique including, but not limited to the disclosed techniques described in Examples 4, 5, 6 and 7 of the specification. The Court finds that one of ordinary skill in the art as of December 1987 would have understood from the specification that the inventors' method combined target capture and all manner of non-specific amplification, including the disclosed

examples.

260. Gen-Probe further submits that the Court should construe the term "amplification" as used in the '338 patent to encompass only the process of creating multiple double-stranded copies of the target polynucleotide or multiple transcripts made from a double-stranded and not to include the mere creation of a single complementary transcript copy of a target strand.

c. "Target Polynucleotide" of the Claims Encompasses DNA and RNA of any desired sequence.

261. The '338 patent describes a target polynucleotide as either DNA or RNA, having a base sequence of particular interest indicative of pathogens, genetic conditions, or desirable gene characteristics." ('338 patent, col. 2; l. 59 – col. 3, l. 5.) Again, without further limitation, that term should be given its defined meaning without restriction to any particular sequence or type of nucleic acid. *See, e.g., Vitronics Corp. supra,* 90 F.3d at 1582 .

d. As properly construed, the claims of the '338 patent encompassing non-specific amplification of any desired sequence of DNA or RNA are invalid for lack of enablement.

The specification does not enable the full breadth of the claims.

262. Section 112 requires that a patent's teachings must be commensurate in scope with the breadth of each claim. *See e.g., Genentech, Inc. v. Novo Nordisk, A/S*, 108 F.3d 1361, 1365 (Fed. Cir. 1997). Logically, therefore, the scope of the claims must be less than or equal to the scope of the enablement; otherwise, the claims are invalid. *See, e.g., Nat'l Recovery*, 166 F.3d at 1196.

263. The evidence in this case that shows that the inventors and their colleagues did not – and could not – enable the successful practice of the non-specific exponential amplification techniques of Examples 6 and 7. Similarly, the evidence in this case that shows that the inventors and their colleagues did not – and could not – enable the successful practice of the non-specific linear amplification techniques of Examples 4 and 5.

264. As set forth above, by the claimed filing date of the disclosure of the invention on December 21, 1987, Gene Trak scientists had not successfully performed the non-specific amplification technique disclosed in Example 6. Despite over 5 months of dedicated effort, those

skilled scientists, who met or exceeded the level of ordinary skill, concluded that the technique simply would not work. Because they were using far more detailed methods and techniques than disclosed in Example 6, clearly the specification failed to provide the necessary teaching to satisfy Section 112. Because inventors are presumed to possess insight or knowledge beyond the "conventional wisdom" possessed by a person of ordinary skill in the art, *Standard Oil Co. v. American Cyanamid Co.*, 774 F.2d 448, 454 (Fed. Cir. 1985), Gene Trak's undisclosed internal failure to perfect Example 6 is powerful evidence of its lack of enablement.

265. As to Example 7, to this day, no scientist from either Gene Trak or Vysis has ever even *attempted* this technique. Given the great scientific and commercial value that would derive from any successful implementation of this claimed technique, their absolute failure to pursue their own alleged invention speaks volumes as to the reason for that lack of effort.

266. Vysis also cannot dispute that the mere disclosure of Blumenthal's prior art paper does not provide sufficient teaching to enable the practice of either linear or exponential amplification techniques of Example 7 across the full spectrum of potential target polynucleotide sequences. As noted above, that paper merely confirms the extensive experimentation required to achieve even partial copying of a few selected nucleic acids. Blumenthal does not provide a disclosure sufficient to enable even linear amplification across the full spectrum of claimed nucleic acids and provides no teaching whatsoever of the claimed use of Qß replicase for exponential amplification. Indeed, to this day, there are no published reports of the successful use of Qß replicase to perform either linear or exponential amplification across the full spectrum of target nucleic acids.

267. This lack of enablement of Examples 6 and 7 is even more significant when the Court considers the "promised" disclosure of those Examples. While Examples 4 and 5 purport to disclose linear amplification only, Examples 6 and 7 represent the *only* disclosure of the *only* commercially viable amplification techniques encompassed by the patent.[4] Consequently,

[4] The linear amplification methods of Examples 4 and 5 are largely irrelevant. Only exponential amplification has significant utility. Vysis' own expert, Dr. David Persing has characterized exponential amplification as "the hallmark of a nucleic acid amplification method." Dr. Persing, "In Vitro Nucleic Acid Amplification Techniques," Diagnostic Molecular Microbiology at 51 (1993). In any event, as set forth in Section II, above, no scientist at Gene Trak ever attempted the

although Gene Trak's failure to enable 50% of the disclosed preferred embodiments should be singularly sufficient to render the claims invalid, its failure to enable 100% of the commercially viable claims should be conclusive. Further, the same considerations that demonstrate lack of enablement of Examples 6 and 7 suggest lack of enablement of Examples 4 and 5.

268. The claims of the '338 patent are therefore invalid for lack of enablement.

2. Obviousness, Anticipation and Prior Public Disclosure.

269. Section 103 of the Patent Act provides that "[a] patent may not be obtained . . . if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103. Consistent with the language of the statute, the Federal Circuit has confirmed that trial courts must consider the invention as a whole and consider the claims in their entirety. *See, e.g., W.L. Gore & Assocs. v. Garlock, Inc.*, 721 F.2d 1540, 1551 (Fed. Cir. 1983); *Medtronic, Inc. v. Cardiac Pacemakers, Inc.*, 721 F.2d 1563, 1567 (Fed. Cir. 1983). The Federal Circuit has repeatedly confirmed that the issue of obviousness is based upon factual determinations. *See, e.g., Monarch Knitting Machinery Corp. v. Sulzer Morat GMBH*, 139 F.3d 877, 881 (Fed. Cir. 1998) ("Obviousness is ultimately a determination of law based on underlying determinations of fact."); *Richardson-Vicks, Inc. v. Upjohn Co.*, 122 F.3d 1476, 1479 (Fed. Cir. 1997). Those factual determinations include: (1) the scope and content of the prior art; (2) the differences between the prior art and the properly construed claims; (3) the level of ordinary skill in the art at the time of the invention; and (4) objective evidence of non-obviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18, 86 S.Ct. 684, 693-94 (1966).

270. Where it is contended that multiple references, considered together, make the invention obvious, the relevant inquiry for determining the scope and content of the prior art is "whether there is a reason, suggestion, or motivation in the prior art or elsewhere that would have led one of ordinary skill in the art to combine the references." *Ruiz v. A.B. Chance Co.*, 234 F.3d

---

experiments of Example 4 or 5.

654, 664 (Fed. Cir. 2000).

271. In appropriate circumstances, a single prior art reference can render a claim obvious. *Sibia Neurosciences, Inc. v. Cadus Pharmaceutical Corp.* 225 F.3d 1349, 1356 (Fed. Cir. 2000); *B.F. Goodrich Co. v. Aircraft Braking Sys. Corp.*, 72 F.3d 1577, 1582 (Fed. Cir. 1996). A single prior art reference can render a claim obvious if there exists a suggestion or motivation to modify the teachings of that reference to the claimed invention in order to support the obviousness conclusion. *Sibia Neurosciences, supra,* 225 F.3d at 1356; *B.F. Goodrich, supra,* 72 F.3d at 1582.

272. The suggestion or motivation to combine references or to modify the teachings of a single reference may be derived from the prior art reference itself, from the knowledge of one of ordinary skill in the art, or from the nature of the problem to be solved. *Ruiz, supra,* 234 F.3d at 665; S*ibia Neurosciences, supra,* 225 F.3d at 1356.

273. Determining whether there is a suggestion or motivation to combine references or modify a single prior art reference is one aspect of determining the scope and content of the prior art, a fact question subsidiary to the ultimate conclusion of obviousness. S*ibia Neurosciences, supra,* 225 F.3d at 1356.

274. A patent may also be invalid based on anticipation under Section 102 of the Patent Act. 35 U.S.C. § 102(a) provides that one cannot obtain a patent for an invention that "was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for patent." Section 102(a) therefore establishes that a person cannot patent what was already known to others. "If the invention was known to or used by others in this country before the date of the patentee's invention, the later inventor has not contributed to the store of knowledge, and has no entitlement to a patent." *Woodland Trust v. Flowertree Nursery, Inc.*, 148 F.3d 1368, 1370 (Fed. Cir. 1998). Accordingly, in order to invalidate a patent based on prior knowledge or use, that knowledge or use must have been available to the public. *See, e.g., Carella v. Starlight Archery*, 804 F.2d 135, 139 (Fed. Cir. 1986) (the § 102(a) language "known or used by others in this country" means knowledge or use which is accessible to the public); *Constant v. Advanced Micro-Devices, Inc.*, 848 F.2d 1560, 1568 (Fed. Cir. 1988) (The term "printed publication" means that "before the critical date the reference

must have been sufficiently accessible to the public interested in the art . . . .").

275. "[A] claim is anticipated if each and every limitation is found either expressly or inherently in a single prior art reference." *Celeritas Techs., Ltd. v. Rockwell Int'l Corp.*, 150 F.3d 1354, 1360 (Fed. Cir. 1998). Whether a claim limitation is inherent in a prior art reference is a factual issue on which evidence may be introduced. *In re Schreiber*, 128 F.3d 1473, 1477, 44 USPQ2d 1429, 1431 (Fed.Cir.1997). Anticipation is a question of fact, which must be established by clear and convincing evidence. *See Hoover Group, Inc. v. Custom Metalcraft, Inc.*, 66 F.3d 299, 302 (Fed. Cir. 1995); *Shearing v. Iolab Corp.*, 975 F.2d 1541, 1544 (Fed. Cir. 1992).

276. "Anticipation" and "obviousness" are determined as of the date of the invention, which is presumed to be the filing date of the patent application. *Ecolochem, Inc. v. Southern California Edison Co.*, 227 F.3d 1361, 1371 (Fed. Cir. 2000); *Gamma-Metrics, Inc. v. Scantech Ltd.*, 52 USPQ2d 1579, 1585 (S.D. Cal. 1998).

277. Under 35 U.S.C. § 102(b), a patent is invalid if the invention was described in a printed publication in any country more than one year prior to the date of the application for the patent in the United States.

a. Vysis' claim of priority for the '338 patent is invalid and the effective filing date of the '080 application is no earlier than January 31, 1991.

278. The '338 patent issued from U.S. patent application no. 08/238,080 (the " '080 application"), filed May 3, 1994. However, Vysis contends that the '080 application is entitled to claim the benefit of at least five prior patent applications and thus to an effective filing date of December 21, 1987.

279. Gen-Probe disputes that the '080 application is entitled to ***any*** filing date earlier than the date of the '080 application itself, and alternatively contends that the '080 application is not entitled to any filing date earlier than January 31, 1991, the filing date of U.S. patent application 07/648,468.

280. 35 U.S.C. § 120 sets forth the requirements that must be met before an application is entitled to the benefit of an early filing date in the United States. The requirements include the following: First, the application must be "for an invention disclosed in the manner provided by the

first paragraph of section 112 . . . in an application previously filed in the United States;" second, the application which claims the benefit must be co-pending with the earlier application or with an application which is itself entitled to the benefit of the earlier date; and third, there must be a "specific reference" in the later filed application to the "earlier filed application."

281. Vysis has the burden of proving that the requirements of 35 U.S.C. § 120 have been satisfied by each prior patent application in the chain of applications that make up its claim of priority and that it is therefore entitled to claim the benefit of December 21, 1987 as the filing date. *Kubota v. Shibuya,* 999 F.2d 517, 521 (Fed.Cir. 1993); *Bloch v. Chiatse Sze,* 484 F.2d 1202 (CCPA 1973).

282. As part of its claim of priority for the '338 patent, Vysis claims that U.S. patent application 07/136,920 is entitled to the benefit of earlier-filed application 06/922,155. However, the '920 application is not entitled to the benefit of the filing date of the '155 application under 35 U.S.C. § 120 because the '155 application does not disclose the invention claimed in the '920 application in the manner provided by the first paragraph of 35 U.S.C. § 112.

283. As part of its current claim of priority for the '338 patent, Vysis claims that U.S. patent application 07/648,468 is entitled to the benefit of earlier-filed application 07/644,967. However, the '468 application is not entitled to the benefit of the filing date of the '967 application, for several reasons.

284. First, under 35 U.S.C. §§ 120 and 133, the post-abandonment amendment made by Vysis to the '468 application to claim priority from the '867 application is legally invalid, null, and void because Vysis did not revive the '468 application pursuant to 35 U.S.C. § 133 and 37 C.F.R. § 1.137(a) or pursuant to 35 U.S.C. § 41(a)(7) and 37 C.F.R. § 1.1.37(b) and did not make the amendments in good faith and with honesty. An abandoned intermediate patent application may not be amended after patent issuance without the applicant seeking revival of such application and satisfying the requirements of the applicable revival regulations. Congress has required that such applications be deemed "abandoned" (35 U.S.C. § 133). Congress and the Commissioner have provided that abandoned applications may be "revived" only when certain particular requirements are met. (35 U.S.C. §§ 41(a)(7), 133; 37 C.F.R. § 1.137.) Vysis did not petition to revive the

applications prior to amending them and could not have satisfied the statutory and regulatory requirements for revival. Vysis simply made amendments to the abandoned applications, without reviving them. While the PTO entered the amendments, such entry was invalid under 35 U.S.C. § 133. *Baxter International, Inc. v. McGaw, Inc.*, 19 F.3d 1321, 1334 (Fed. Cir. 1998); *Exxon Corp. v. Phillips Petroleum*, 1999 U.S. Dist. Lexis 20806 (S.D. Tex. 1999). Section 133 expressly provides that an application must be regarded as abandoned if the application fails to prosecute the application within 6 months of any action by the PTO. Section 133 sets forth a congressional mandate. Any application which is to be "regarded as abandoned" pursuant to 35 U.S.C. § 133 must be treated by the PTO and the courts as abandoned. *Lindsay v. Stein*, 10 F. 907, 913 (C.C.N.Y. 1882). The abandonment of an application results in the ***final*** termination of ***all*** proceedings on the application. *Manual of Patent Examining Procedures ("MPEP")* § 201.11 at 200-53 (Rev 1., Feb. 2000); *see also MPEP* § 203.05 at 200-77 (Rev 1., Feb. 2000) (Abandoned applications are immediately removed from the PTO docket of pending applications); *accord*, 4 *Chisum on Patents* § 13.05 at 13-41 (2000). An abandoned application cannot be regarded as available for amendment:

> An application which is to be 'regarded as abandoned' must be regarded as abandoned by the commissioner and the courts, and, if it is regarded as abandoned, it cannot be regarded as subsisting ...

Lindsay v. Stein, 10 F. 907, 913 (C.C.N.Y. 1882). Or, to be put more bluntly, abandonment of a patent application turns it into a "dead body." *Struthers Patent Corp. v. Nestle Co.*, 558 F. Supp. 747, 811 (D.N.J. 1981), *aff'd*, 709 F.2d 1493 (3d Cir. 1982), *cert. denied*, 464 U.S. 915 (1983). Congress has provided two statutes that permit an applicant to revive an abandoned application. First, 35 U.S.C. § 133 provides that, if an applicant fails to prosecute an application within a specified time, then the application shall become abandoned, "unless it be shown to the satisfaction of the Commissioner[5] of the Patent and Trademark Office that such delay was unavoidable." 35 U.S.C. § 133. Pursuant to this statute, the Commissioner has enacted a comprehensive set of

[5] Effective March 29, 2000, the Commissioner of the PTO became known as the "Director" of that office. However, because the statutes and cases cited in this memorandum uniformly use the former title, the term "Commissioner" will be used here for clarity's sake.

regulations governing the procedures and substantive requirements for revival. 37 C.F.R. § 1.137 (a). Second, a more recently enacted statute, 35 U.S.C. § 41(a)(7), provides that an applicant may file a petition for revival of an "unintentionally abandoned" application. The Commissioner has also adopted a comprehensive set of regulations governing the procedures and substantive requirements for revival under this statute. 37 C.F.R. § 1.137 (b). An abandoned intermediate patent application may not be amended after patent issuance without the applicant seeking revival of such application and satisfying the requirements of the applicable revival regulations. 35 U.S.C. § 133. *See also Air Products and Chemicals v. Quigg*, 8 USPQ2d 2015 (D.D.C. 1988); *Sampson v. Ampex Corp.*, 335 F.Supp. 242 (S.D.N.Y. 1971), *aff'd*, 463 F.2d 1042 (2d Cir. 1972); *In re Application G*, 11 USPQ2d 1378 (Commr. Pat 1989). Otherwise, such an application must be regarded as truly abandoned, a "dead body," and not available for amendment. The PTO's own rules recognize that:

> When an amendment is filed after the expiration of the statutory period [for response to a PTO rejection], the application is abandoned ***and the remedy is to petition to revive it.***

MPEP § 711.02 at 700-84 (Rev 1., Feb. 2000). The Board of Patent Appeals and courts have refused to recognize amendments made to abandoned patent applications. See, e.g., *Lorenz v. Finkl*, 333 F.2d 885, 895-896 (C.C.P.A. 1964); *Struthers Patent Corp. v. Nestle Co.*, 558 F.Supp. 747, 811 (D.N.J. 1981), *aff'd*, 709 F.2d 1493 (3d Cir. 1982), *cert. denied*, 464 U.S. 915 (1983). As applied to this case, the regulations and cases show that the intermediate patent application was required by 35 U.S.C. § 133 to be regarded as abandoned and thus "dead" for all purposes unless revived according to the statute and regulations. Given that defendant Vysis never attempted to revive these applications, Vysis could not amend these applications to change the priority claim. Furthermore, if an abandoned application may be amended without revival, amendment may be permitted only if the applicant has conducted itself at all times with good faith and honesty, a standard that Vysis cannot meet. Because Vysis' amendments to these applications are null and void, the applications do not contain the required "specific reference" to earlier-filed applications that is essential for such applications to provide priority under section 120.

285. Second, U.S. patent application 07/648,468 is not entitled to the benefit of the filing

date of the '967 application because the claims of the '468 application are not disclosed in the '967 application in the manner provided by the first paragraph of 35 U.S.C. § 112, as required by 35 U.S.C. § 120. Section 120 gives the benefit of a prior application's filing date only to the "invention" that is the subject to the later application, *if* that particular invention was adequately disclosed in the prior application. At least one claim of the subsequent application must be disclosed in the prior application in order for the subsequent application to have the benefit of the filing date of the earlier application under section 120. *Martin v. Johnson*, 454 F.2d 746, 750 (CCPA 1972); *In re Scheiber*, 199 USPQ 782, 784 (CCPA 1978); *In re Lukach*, 442 F.2d 967, 968, 169 USPQ 795, 796 (1971); *In re Brower*, 433 F.2d 813, 817, 167 USPQ 684, 687 (1970); *In re Kirchner*, 305 F.2d 897, 900, 904 (CCPA 1962); Chisum on Patents § 13.02 [4] at 13-11 (1999). No claim of the '468 application is disclosed in the '967 application in the manner provided by the first paragraph of 35 U.S.C. § 112. In order for a patent application to be entitled to the benefit of the filing date of an earlier application, the prior application must disclose the invention claimed in the subsequent application sufficiently to provide an adequate written description of the invention:

> An application for a patent for an invention **disclosed in the manner provided in the first sentence of section 112 of this title in an application previously filed in the United States** by the same inventor ... shall have the same effect, **as to such invention**, as though filed on the date of the prior application....

35 U.S.C. § 120. The chain of patent applications relied on by Vysis for its claim of priority for the '338 patent fail to satisfy this requirement of section 120. The PTO repeatedly recognized that the invention of the '468 application was not disclosed in the prior '920 application.

286. Third, U.S. patent application 07/648,468 is not entitled to the benefit of the filing date of the '967 application with respect to later-filed method claims in light of the fact that the '468 application was filed in response to a restriction requirement by the U.S. Patent and Trademark Office and the applicant was thereafter required to act consistently (i.e., maintain consonance) with such election. *Gerber Garment Technology Inc. v. Lectra Systems Inc.*, 16 USPQ2d 1437, 1440-1441 (Fed. Cir. 1990); *Pennwalt Corp. v. Akzona Inc.*, 222 USPQ 833 (Fed. Cir. 1984).

287. As part of a previous claim of priority for the '338 patent, Vysis contended that U.S. patent application 07/648,468 was directly entitled to the benefit of earlier-filed application 07/136,920. Vysis no longer makes such a contention of direct benefit. If such a contention is re-instituted, the '468 application is not directly entitled to the benefit of the filing date of the '920 application, for several reasons.

288. First, the '920 application was not pending at the time the '468 application was filed.

289. Second, the '468 application would not be entitled under 35 U.S.C. § 120 to the earlier filing date of the '920 application in light of the fact that no claim of the '468 application is disclosed in the '920 application in the manner provided by the first paragraph of 35 U.S.C. § 112. At least one claim of the subsequent application must be disclosed in the prior application in order for the subsequent application to have the benefit of the filing date of the earlier application under section 120. *Martin, supra*, 454 F.2d at 750; *In re Scheiber, supra,* 199 USPQ at 784; *In re Lukach, supra,* 442 F.2d at 968, 169 USPQ at 796; *In re Brower, supra,* 433 F.2d at 817, 167 USPQ at 687; *In re Kirchner, supra,* 305 F.2d at 904; Chisum on Patents § 13.02 [4] at 13-11 (1999).

290. Third, the '468 application would not be entitled to the benefit of the filing date of the '920 application with respect to later-filed method claims in light of the fact that the '468 application was filed in response to a restriction requirement by the U.S. Patent and Trademark Office and the applicant was thereafter required to act consistently (i.e., maintain consonance) with such election. *Gerber Garment Technology Inc. v. Lectra Systems Inc.*, 16 USPQ2d 1437, 1440-1441 (Fed. Cir. 1990); *Pennwalt Corp. v. Akzona Inc.*, 222 USPQ 833 (Fed. Cir. 1984).

291. As part of its current claim of priority for the '338 patent, Vysis claims that U.S. patent application 07/946,749 is indirectly entitled to the benefit of the earlier-filed application '967 application. However, the '749 application is not entitled to the benefit of the filing date of the '967 application, for several reasons.

292. First, under 35 U.S.C. §§ 120 and 133, the post-abandonment amendment made by Vysis to the '749 application to include a specific reference to the '967 application is legally

invalid, null, and void for the reasons set forth hereinabove.

293. Second, the '749 application is not entitled to the benefit of the filing date of the '967 application because no claim in the '468 and '749 applications was disclosed in the '967 application in the manner provided by the first paragraph of 35 U.S.C. § 112, as set forth hereinabove.

294. Third, the '749 application is not entitled to the benefit of the filing date of the '967 application with respect to later-filed method claims in light of the fact that the '468 and '749 applications were filed in response to a restriction requirement by the Patent Office and the applicant was thereafter required to act consistently (i.e., maintain consonance) with such election, as set forth hereinabove.

295. As part of its current claim of priority for the '338 patent, Vysis claims that U.S. patent application 08/124,826 is indirectly entitled to the benefit of the earlier-filed application '967 application. However, the '826 application is not entitled to the benefit of the filing date of the '967 application, for several reasons.

296. First, under 35 U.S.C. §§ 120 and 133, the post-abandonment amendment made by Vysis to the '826 application to include a specific reference to the '967 application is legally invalid, null, and void for the reasons set forth hereinabove.

297. Second, the '826 application is not entitled to the benefit of the filing date of the '967 application because no claim in the '468, '749, and '826 applications was disclosed in the '967 application in the manner provided by the first paragraph of 35 U.S.C. § 112, as set forth hereinabove.

298. Third, the '826 application is not entitled to the benefit of the filing date of the '967 application with respect to later-filed method claims in light of the fact that the '468, '749 and '826 applications were filed in response to a restriction requirement by the Patent Office and the applicant was thereafter required to act consistently (i.e., maintain consonance) with such election, as set forth hereinabove.

299. As part of its current claim of priority for the '338 patent, Vysis claims that U.S. patent application 08/238,080 is entitled to the benefit of the earlier-filed application '826

application. However, the '080 application is not entitled to the benefit of the filing date of the '826 application, for several reasons.

300. First, the certificate of correction obtained by Vysis after the issuance of the '338 patent, changing the claim of priority from U.S. patent application 08/400,657 to U.S. patent application 08/124,826 is invalid and ineffective because that certificate of correction could not and did not amend the '080 application itself. The certificate therefore did not change the effective date of the '080 application under the literal language of 35 U.S.C. § 120, which requires that the application for the patent be amended. *See Sampson v. Ampex Corp.*, 333 F.Supp. 59, 63 (S.D.N.Y. 1971).

301. Second, the certificate of correction obtained by Vysis after the issuance of the '338 patent, changing the claim of priority from U.S. patent application 08/400,657 to U.S. patent application 08/124,826 is invalid because Vysis' request for the certificate of correction did not meet the statutory requirements for a certificate of correction under 35 U.S.C. § 255. Section 255 permits a patentee to seek a certificate of correction "whenever a mistake of a clerical or typographical nature, or of minor character, which was not the fault of the Patent and Trademark Office, appears in a patent and a showing has been made that such mistake occurred in good faith." In *Superior Fireplace Co. v. Majestic Products Co.*, 270 F.3d 1358, 1375 (Fed. Cir. 2001), the Federal Circuit interpreted the statutory requirement that a mistake subject to "correction" be one "of minor character." In affirming the district court's summary judgment that the certificate of correction obtained by the patentee was invalid, the Federal Circuit held that a mistake that, if corrected, would avoid certain invalidity of the patent "must be viewed as highly important and thus ***cannot be a mistake of minor character.***" *Superior Fireplace, supra,* 270 F.3d at 1375 (emphasis added). Under this precedent, as a matter of law, a substantive change to a patentee's claim of priority that saves a patent from invalidity cannot qualify as a "a mistake of minor character." *Superior Fireplace, supra,* 270 F.3d at 1375 ; *see also In re Arnott*, 19 USPQ2d 1049 (Comm'r Pat. Trademarks 1991). The '080 application's claim of priority to the '826 application was not "a mistake of a clerical or typographical nature, or of minor character." *Superior Fireplace, supra,* 220 F.3d at 1376; *In re Arnott, supra,* 19 USPQ2d at 1049; *See also Brenner v.*

State of Israel, 400 F.2d 789, 158 USPQ 584 (D.C. Cir. 1968). Additionally, the mistake was not inadvertent. Vysis made deliberate, reasoned choices with respect to its claim of priority to the '657 application. A deliberate choice does not result in a "mistake" within the scope of 35 U.S.C. § 255. See *In re Orita*, 550 F.2d 1277, 193 USPQ 145 (C.C.P.A. 1977) (applicant could not establish "inadvertence, accident, or mistake" for purposes of reissue where defect resulted from deliberate choice); *In re Mead*, 198 USPQ 412 (C.C.P.A. 1978) (same). Furthermore, if the '080 application's claim of priority to the '826 application was "a mistake of a clerical or typographical nature, or of minor character," such mistake did not occur in good faith. The applicant's overall course of conduct with respect to the prosecution of applications for the '338 patent, particularly after the abandonment of the '505 application, demonstrates the applicant's lack of good faith. If the certificate of correction is valid and effective, it does not apply to Gen-Probe. Gen-Probe acquired intervening rights prior to issuance of certificate of correction. A certificate of correction does not affect causes of action that accrued before it was issued. *Southwest Software Inc. v. Harlequin Inc.*, 56 USPQ2d 1161 (Fed. Cir. 2000).

302. Third, no claim of the '080 application is disclosed in the '826 application in the manner provided by the first paragraph of 35 U.S.C. § 112, as required by 35 U.S.C. § 120. At least one claim of the subsequent application must be disclosed in the prior application in order for the subsequent application to have the benefit of the filing date of the earlier application under section 120. *Martin, supra*, 454 F.2d at 750; *In re Scheiber, supra*, 199 USPQ at 784; *In re Lukach, supra,* 442 F.2d at 968, 169 USPQ at 796; *In re Brower, supra,* 433 F.2d at 817, 167 USPQ at 687; *In re Kirchner, supra,* 305 F.2d at 900, 904; Chisum on Patents § 13.02 [4] at 13-11 (1999). Adequate "disclosure" under sections 120 and 112 with respect to an invention claimed in a prior application may not be accomplished solely by a conclusory boilerplate "incorporation by reference." *Maine Manufacturing Co. v. U.S. International Trade Commission*, 37 USPQ2d 1609, 1614 (Fed. Cir. 1996); *Ex Parte Raible*, 8 USPQ2d 1709, 1710 (Bd. Pat App. 1988); *Ex Parte McGrath*, 109 USPQ 70, 72 (Bd. Pat. App. 1955). Conclusory boilerplate "incorporation by reference" is particularly ineffective for purposes of section 120 when the earlier application was filed in response to a restriction requirement by the PTO, for such incorporation violates principles

of consonance, *see Gerber Garment Technology Inc. v. Lectra Systems Inc.*, 16 USPQ2d 1437, 1440-1441 (Fed. Cir. 1990); *Pennwalt Corp. v. Akzona Inc.*, 222 USPQ 833 (Fed. Cir. 1984), and where the inventors on the two applications are not the same.

303. Fourth, the '080 application is not entitled to the benefit of the filing date of the '826 application in light of the fact that the '468 application and all subsequent device applications were filed in response to a restriction requirement by the Patent Office and the applicant was thereafter required to act consistently (i.e., maintain consonance) with such election. *Gerber Garment Technology Inc. supra*, 16 USPQ2d at 1440-1441; *Pennwalt Corp., supra*, 222 USPQ at 833.

304. As part of a previous claim of priority for the '338 patent, Vysis contended that the '080 application was entitled to the benefit of application 08/400,657. Vysis no longer makes such a contention. If such a contention is re-instituted, the '080 application is not entitled to the benefit of the filing date of the '657 application, for several reasons.

305. First, the '657 application was not pending at the time the '080 application was filed. 35 U.S.C. § 120.

306. Second no claim of the '080 application is disclosed in the '657 application in the manner provided by the first paragraph of 35 U.S.C. § 112 as required by 35 U.S.C. § 120, as discussed hereinabove.

307. To the extent that Vysis claims that the '468 application was filed at least in part as a divisional application to the '920 application in response to the Patent Office's restriction requirement in the '920 application, the '080 application is still not entitled to the benefit of the filing date of the '657 application in light of the fact that the such a claim to priority would be inconsistent with that prior election, as discussed hereinabove.

b. The '338 patent is invalid under 35 U.S.C. § 102(b) in light of the public disclosure of the invention on August 23, 1989.

308. Because the priority date of the '338 patent is no earlier than January 31, 1991, the patent is invalid pursuant to 35 U.S.C. § 102(b) in light of the public disclosure on August 23, 1989 of the invention claimed in the '338 patent, upon publication of Vysis' application for European

Patent publication no. 0 328 829 A2. *Baxter International, Inc. v. McGaw, Inc.*, 149 F.3d 1321 (Fed. Cir. 1998).

309. Furthermore, even ignoring the procedural defects that should limit the priority date to January 31, 1991, to the extent that the Court determines that Vysis' priority date is limited to May 24, 1994 (the filing date of the '080 application), the above-referenced publication of the PCT application corresponding to the '338 patent would similarly render the '338 patent invalid under 35 U.S.C. 102(b).

c. The invention claimed in the '338 patent is obvious and anticipated even if the effective filing date of the '080 application is December 21, 1987.

310. The invention claimed in the '338 Patent would have been obvious to one of ordinary skill in the art as of December 21, 1987, if the '338 patent is entitled to such filing date. Specifically, and as set forth in Section II, above, before December 21, 1987, it was common practice to isolate a target polynucleotide from a sample by contacting the sample with a solid support that bound to the target polynucleotide either directly or indirectly. The support with its attached polynucleotide and bound target polynucleotide was separated from the sample, effectively separating the target from other sample components that could interfere with further manipulation of the target polynucleotide. It was also well known in the art that amplifying the target polynucleotide directly or by producing an amplified signal based upon the presence of the target polynucleotide could increase detection sensitivity. It would have been obvious to one of ordinary skill in the art in December 1987 to perform the combination of those manipulations for the purpose of detecting the presence of a target polynucleotide in a sample. One of ordinary skill would have been motivated to combine both target polynucleotide capture and amplification to ensure success in a detection assay.

311. The examples of the '338 patent that disclose amplification disclose only non-specific amplification of the target polynucleotide. Particularly where the amplification method to be used is non-specific, it would have been obvious to one of ordinary skill in the art to use a specific capture step prior to amplification. Prior to December 21, 1987, it was well known to those skilled in the art that specificity had to be provided in some step of every biologic assay.

Prior to December 21, 1987 it was known that nucleic acid sequences could be attached to solid supports such as magnetic beads in order to specifically capture a complementary nucleic acid of interest. Thus as of December 27, 1987, it would have been obvious to one skilled in the art to use a specific capture step to isolate the target nucleic acid prior to non-specific amplification. Unless the target was isolated, non-specific amplification would not solve the problem that amplification was originally intended to address. Non-specific amplification of an entire sample, without a separation step, would not be likely to increase the amount of signal over background generated by the hybridization of detector probe to target. This was known by those of ordinary skill in the art and was also disclosed in the prior art as of December 21, 1987.

312. In addition to being obvious, the claimed invention of the '338 patent is anticipated by each of Arsenyan et al., Gaubatz et al., Powell et al., Chu, et al and Feix et al. 1987.

313. There are no relevant secondary considerations of non-obviousness in this case other than Vysis' own lack of commercial success. Secondary considerations are relevant, if at all, only when they directly relate to the invention(s) expressly claimed in the patent at issue. *See, Sjolund v. Musland*, 847 F2d 1573, 1582 (Fed. Cir. 1988); *In re Vamco Machine & Tool, Inc.*, 752 F.2d 1564, 1577 (Fed. Cir. 1985). Gen-Probe's products, and its conduct with respect to TMA technology, are irrelevant because they do not involve the claimed invention. Further, Gen-Probe's conduct and products are remote in time to the alleged date of invention. Vysis cannot show the required nexus between the license obtained by Gen-Probe and the merits of invention claimed in the '338 patent. *In re GPAC, Inc.*, 57 F.3d 1573, 1580 (Fed. Cir. 1995).

C. THE '338 PATENT IS UNENFORCEABLE ON THE GROUND OF PROSECUTION LACHES.

314. Applicants intentionally, unreasonably, and inexcusably delayed in the prosecution of the invention claimed in the '338 patent. Gen-Probe was injured by such delay.

315. The equitable doctrine of laches bars enforcement of patent claims that were issued following unreasonable and unexplained delay, where such delay causes injury to an alleged infringer and others.

316. The intent of the patent statute has always been to grant patent rights for a limited

time. The law has not approved of delays before filing and during prosecution which extend the period of patent rights or otherwise injure others. Any practice by inventors through which they deliberately and without excuse postpone the beginning of the patent monopoly is an evasion of the patent statute and defeats it benevolent aim. *In re Bogese*, 22 USPQ2d 1821 (Comr Pat. 1991).

D. THE '338 PATENT IS UNENFORCEABLE DUE TO INEQUITABLE CONDUCT BY APPLICANTS.

317. Applicants for patents have a duty to prosecute patent applications in the Patent Office with candor, good faith, and honesty. *Li Second Family Limited Partnership v. Toshiba Corp.*, 231 F.3d 1373, 1378 (Fed. Cir. 2000); 37 C.F.R. § 1.56.

318. A breach of this duty, which breach can include affirmative misrepresentations of material facts, failure to disclose material information, or submission of false material information, coupled with an intent to deceive, constitutes inequitable conduct. *Li Second Family Limited Partnership, supra*, 231 F.3d at 1378 . Inequitable conduct renders a patent unenforceable. *Id.*

319. Inequitable conduct requires a showing by clear and convincing evidence that the alleged nondisclosure or misrepresentation occurred, that the nondisclosure or misrepresentation was material, and that the patent applicant acted with the intent to deceive the PTO. *Id.* Once the threshold levels of materiality and intent have been established, the trial court must weigh materiality and intent to determine whether the equities warrant a conclusion that inequitable conduct occurred. *Id.*

320. The more material the information misrepresented or withheld by the applicant, the less evidence of intent will be required in order to find that inequitable conduct has occurred. *Id.*

321. Information is deemed material if there is a substantial likelihood that a reasonable examiner would have considered the information important in deciding whether to allow the application to issue as a patent, not whether the information would conclusively decide the issue of patentability. *Id.* at 1379-1380. Information concealed from the PTO may be material even though it would not invalidate the patent.

322. Materiality is not limited to "prior art," but instead embraces any information that a reasonable examiner would be substantially likely to consider important in deciding whether to

allow an application to issue as a patent. *GFI, Inc. v. Franklin Corp.*, 265 F.3d 1268, 1274 (Fed. Cir. 2001); *Akron Polymer Container Corp. v. Exxel Container, Inc.*, 148 F.3d 1380, 1382 (Fed. Cir. 1998).

323. Because the effective filing date of each claim in a patent application determines which references are available as prior art for purposes of §§ 102 and 103, information regarding the effective filing date is of the utmost importance to an examiner. Consequently, an applicant's misrepresentation that he is entitled to the benefit of an earlier filing date is highly material. *Id.* at 1380.

324. Intent to deceive the PTO need not be proven by direct evidence. Indeed, direct proof of wrongful intent is rarely available but may be inferred from clear and convincing evidence of the surrounding circumstances. *Id.* The intent element of the offense is therefore in the main proven by inferences drawn from facts, with the collection of inferences permitting a confident judgment that deceit has occurred. *GFI, Inc., supra*, 265 F.3d at 1274.

325. When it is undisputed that a patent applicant was aware of a key reference and had otherwise been exposed to the work of the author of that reference, a strong case for deceptive intent is presented. *See, e.g., Id.* at 1274.

1. The applicants engaged in inequitable conduct with respect to their claim of priority for the '338 patent.

326. The applicants breached their duty of candor, good faith, and honesty to the Patent Office with respect to their claim of priority for the '338 patent by, among other things:

- Asserting a claim of priority for the '338 patent that claimed the benefit of a filing date of December 21, 1987.
- Failing to disclose and call attention to the abandonment of the '505 application in the course of prosecuting the '080 application.
- Failing to disclose and call to the Patent Office's attention, when claiming the '080 application as a divisional application from the '657 application, that the Patent Office had not imposed a restriction requirement as to the '657 application, that the '657 application did not disclose the invention of the '080 application, and that the '657 application was not pending at the time the '080 application was filed.
- Failing to maintain consonance with the segregation of the method and device inventions after the filing of applications 944,505 and 648,468, by amending application no. 238,080 to allege that it was a divisional of application no.

400,657.

- Failing to maintain consonance with the segregation of the method and device inventions after the filing of applications 944,505 and 648,468, by changing the priority claim of the '338 patent to assert that the '080 application was a continuation of application no. 124,826.

- Engaging in the conduct described above with respect to the post-abandonment amendments to the '468, '749, and '826 applications.

- Engaging in the conduct described above with respect to the certificate of correction for the '338 patent.

327. The breaches alleged concerned material information and applicants' conduct was undertaken with the intent to deceive.

2. The applicants engaged in inequitable conduct by failing to disclose material references and misrepresenting the state of the art.

328. As noted in Section II, above, other facts evidencing inequitable conduct exist which render the '338 patent unenforceable. For example, during prosecution of the '080 application, material information known to the applicants that should have been disclosed to the Patent Office was not, in breach of the duty of candor. (See Paragraphs 183 through 204.) Further, applicants intentionally misrepresented the state of the art to the Patent Office (as discussed above).

329. Applicants' breaches of their duty of candor concerned material information and applicants' conduct was undertaken with the intent to deceive.

3. The applicants engaged in other inequitable conduct.

330. The non-enabling disclosures of the '338 patent also provide evidence of the applicants' inequitable conduct. For example, as discussed above, Example 7 is not enabling in that as of December, 1987, the superficial disclosures of Example 7 of the '338 patent did not enable one of ordinary skill in the art to use Qß replicase to exponentially amplify heterologous RNAs. Example 7 constitutes a false example and a person of ordinary skill in the art, including the inventors of the '338 patent, would have known it was false.

331. Moreover, a reasonable examiner has no way of ascertaining whether or not a prophetic example, such as Example 7 is true or false. Accordingly, the examiner must assume it

is true. *See* Manual of Patent Examining Procedure (MPEP) §2164.04. In other words, when Example 7, which is a complete example, states, "Because the replication product is a template for the enzyme, the RNA is replicated exponentially.", the examiner is required by Patent Office policy to accept the statement as true unless the examiner has solid evidence to the contrary. When, as here, a patent applicant files a statement of operability in a patent application when the applicant is aware, at the time the application is filed that, he or she and those of ordinary skill in the art are not capable of operating the invention without undue experimentation, that patent applicant violates the duty of candor.

332. Further evidence of inequitable conduct exists with regard to Example 6 of the '338 patent. As discussed above, Example 6 does not contain sufficient information to permit one of ordinary skill to carry out the amplification process without undue experimentation. Vysis' predecessor understood this to be the fact in that their documents show that Gene-Trak scientists tried but failed to achieve exponential amplification using the random primer amplification method described in Example 6. As a result, the efforts to practice the method set forth in Example 6 were abandoned.

333. Given these circumstances, one of ordinary skill in the art would not have known how to carry out the procedure set forth in Example 6. More importantly, since the applicants were aware of this inoperativeness of Example 6, the inclusion of the example constitutes an affirmative misrepresentation to the Patent Office regarding the scope of the claims.

334. Example 5 also provides evidence of inequitable conduct. The buffer purportedly used in Example 5 specifies concentrations of dNTP reagents that are too high to achieve amplification. Example 5 is therefore inoperative. Its inclusion in the patent constitutes an affirmative misrepresentation to the Patent Office regarding the scope of the claims

E. VYSIS ABANDONED THE INVENTIONS CLAIMED IN THE '338 PATENT.

335. As set forth above, on February 5, 1993, the applicants intentionally abandoned U.S. patent application 07/944,505 with full knowledge of their rights. Applicants thereafter, intentionally and with full knowledge of their rights, took no further action with respect to prosecuting claims for the inventions that had been the subject of the '505 application until May 3,

1994. Applicants elected this course of action (and inaction) in response to rejections by the Patent Office of the '920, '967, and '505 applications, of which certain of the office actions were first action final rejections.

336. Applicants' abandonment of the '505 application and subsequent inaction establish that applicants abandoned the inventions claimed therein in the United States. Applicants were thereafter precluded from obtaining a patent for any such inventions. Section 102 of Title 35, United States Code, provides as follows: "A person shall be entitled to a patent unless - ....(c) he has abandoned the invention ..."

337. Abandonment of the invention may be inferred from conduct that is inconsistent with active prosecution of claims. *United States Rifle & Cartridge Co. v. Whitney Arms Co.*, 118 U.S. 22, 24 (1886); *MacBeth-Evans Glass Co. v. General Electric Co.*, 246 F. 695, 702 (6th Cir. 1917). Therefore, intentional abandonment of a patent application is evidence supporting a contention of abandonment of the invention. *Lorenz v. Finkl*, 333 F.2d 885, 896, 142 USPQ 26 (C.C.P.A. 1964) (Smith, J., concurring); *USM Corp. v. SPS Technologies, Inc.*, 514 F.Supp. 213, 238 (N.D. Ill. 1981).

F. VYSIS HAS COMMITTED ACTS OF UNFAIR COMPETITION.

338. California Business & Professions Code § 17200 provides that "unfair competition shall mean and include any unlawful, unfair or fraudulent business act or practice . . . ." The California Supreme Court has defined "unfair" in the context of § 17200 to mean "conduct that threatens an incipient violation of an antitrust law, or violates the policy or spirit of one of those laws because its effects are comparable to or the same as a violation of the law, or otherwise significantly threatens or harms competition." *Cel-Tech Communications, Inc. v. Los Angeles Cellular Telephone Co.*, 20 Cal.4th 163, 186-87 (1999). Fraud in procuring a patent can give rise to antitrust liability in certain circumstances. *C.R. Bard, Inc. v. M3 Systems, Inc.*, 157 F.3d 1340, 1367 (Fed. Cir. 1998) (citing *Walker Process Equip., Inc. v. Food Mach. & Chem. Corp.*, 382 U.S. 172 (1965)). Conduct prohibited under antitrust law also "includes bringing suit to enforce a patent with knowledge that the patent is invalid or not infringed, and the litigation is conducted for anti-competitive purposes." *C.R. Bard*, 157 F.3d at 1358. Thus, a violation of the "policy or

spirit" of those antitrust laws would give rise to a § 17200 claim.

339. Coverage of unfair competition law has been characterized as "sweeping." *Id.* at 180. In fact, the "unfairness" prong of unfair competition law "is intentionally broad, thus allowing courts maximum discretion to prohibit new schemes to defraud." *Schnall v. Hertz Corp.*, 78 Cal:App.4th 1144 (2000); *see also Dow Chemical Co. v. Exxon Corp.*, 139 F.3d 1470, 1476 (Fed. Cir. 1998) (noting viability of unfair competition claim predicated in part on inequitable conduct).

340. Based on the facts set forth in Section II, above, the facts are clear that the claims of the '338 patent are invalid and unenforceable. Vysis was made aware of these facts when the underlying facts were made known to Vysis by Gen-Probe during discussions concerning settlement of prior, unrelated litigation between the parties. Vysis' enforcement of the '338 patent when it knew or reasonably should have known that the claims of the '338 patent were invalid and unenforceable constitutes unfair competition.

IV. EVIDENTIARY ISSUES

341. Gen-Probe does not presently anticipate any unusual evidentiary issues with the exception that there is a stipulated protective order governing the confidentiality of many of the documents produced by the parties in this action and which relate to highly confidential information concerning the parties' technology, ongoing research programs and collaborations with third parties. Due to the nature of the highly competitive environment in which the parties' operate, the protective order contemplates and directs the method of introduction and use by the parties of confidential information at trial.

342. Gen-Probe anticipates that it may be appropriate to file *in limine* motions concerning the evidence to be offered at trial, but Gen-Probe has not yet identified a complete list of specific issues to be addressed by such motions.

V. BIFURCATION OF ISSUES

343. Due to the importance of and substantial dispute regarding Vysis' claim of priority under 35 U.S.C. § 120 for the '338 patent, Gen-Probe contends that the issues associated with and the determination of the priority should be submitted for trial before the trial of other issues.

344. Gen-Probe contends that the merits of Gen-Probe's unfair competition claim should be reserved and submitted to trial after the trial and determination of other issues.

VI. ABANDONDED ISSUES

345. There are no issues that have been abandoned by stipulation of the parties with the exception of a stipulation between the parties to the effect that Gen-Probe anticipates that its NAT test kits that use a combination of target capture and amplification will enjoy commercial success.

VII. JURY TRIAL

346. Both parties have timely requested a jury trial of all issues so triable.

VIII. WITNESSES

347. The list of witnesses that Gen-Probe presently anticipates offering at trial is set forth on Exhibit "A" hereto.

IX. EXHIBITS

348. The list of exhibits that Gen-Probe presently anticipates offering at the trial of this matter other than those to be used for impeachment are set forth in Exhibit "B" hereto.

Dated: January 14, 2002

STEPHEN P. SWINTON
J. CHRISTOPHER JACZKO
COOLEY GODWARD LLP

R. WILLIAM BOWEN, JR.
GEN-PROBE INCORPORATED

By: 
J. Christopher Jaczko

Attorneys for Plaintiff
GEN-PROBE INCORPORATED